SOME NEWER ASPECTS OF RITTER REACTION
&
DEVELOPMENT OF NOVEL REAGENTS FOR ORGANIC SYNTHESIS

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

By
C. TRINADHA RAO

to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
JULY 1986

to

my mother

and

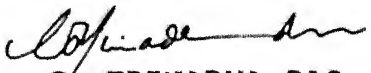
in memory of

my father

STATEMENT

I hereby declare that the matter embodied in this thesis "Some Newer Aspects of Ritter Reaction and Development of Novel Reagents for Organic Synthesis," is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Dr. Y.D. Vankar.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.



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CERTIFICATE

Certified that the work "Some Newer Aspects of Ritter Reaction and Development of Novel Reagents for Organic Synthesis," presented in this thesis has been carried out by Mr. C. Trinadha Rao under my supervision and the same has not been submitted elsehwere for a degree.

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CERTIFICATE OF COURSE WORK

This is to certify that Mr. C. Trinadha Rao has satisfactorily completed all the courses required for the Ph.D. degree program. The courses include:

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Chm 502 Advanced Organic Chemistry II

Chm 511 Physical Organic Chemistry

Chm 524 Modern Physical Methods in Chemistry

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Mr. C. Trinadha Rao was admitted to the candidacy of the Ph.D. degree in January 1982 after successfully completing the written and oral qualifying examinations. Also he has successfully completed his Open Seminar of the work embodied in this thesis.

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The single largest contribution in shaping me what I am, comes from the faith, hope and pride that my mother and sisters have in me. It is their love that kept me going, and I take this opportunity to offer my heartfelt thanks to them.

C. TRINADHA RAO

PREFACE

The thesis deals with two different aspects viz. (i) some newer aspects of Ritter reaction, and (ii) development of novel reagents for organic synthesis, and these separately forms the subject matter of each of the two chapters into which the entire thesis has been divided.

In Chapter I, Ritter reaction, on two different types of carbocationic intermediates that has been carried out by us, is presented in two parts, A & B. To begin with, a brief introduction of the Ritter reaction, illustrating the utility of this reaction in the synthesis of various heterocyclic compounds, including natural products, has been presented.

In Part A, literature survey, including recent aspects dealing with Pummerer rearrangement, is briefly presented as background. Then our studies on trapping of the Pummerer intermediate with nitriles are discussed in detail. It was found that treatment of sulphoxides 43(a-c) and 47 separately with three different nitriles viz., acetonitrile, acrylonitrile and benzonitrile in the presence of a mixture of trifluoroacetic anhydride and trifluoroacetic acid lead to the formation of N-thioaryl/alkyl amides 45(a-g) and 48 in moderate yields, indicating clearly the occurrence of "Ritter reaction on Pummerer intermediate," a detailed mechanism of which is discussed. In cases dealing with aryl sulphoxides 43(a-c), the disulphides

46(a-c) were also isolated alongwith the amides, and a tentative mechanism rationalising their formation has also been proposed.

In part B of Chapter I, a brief literature of the ring opening of cyclopropyl carbinols and ketones, with concomitant attack of nucleophiles, has been presented as background. Our studies involving the reaction of the two cyclopropyl ketones viz., 2-phenylbenzoyl cyclopropane (105) and the cyclopropyl ketone 106 prepared from carvone, and their corresponding alcohols 107 and 108, respectively and 2-phenyl cyclopropane-methanol (109), with acetonitrile and acrylonitrile in the presence of concentrated sulphuric acid have been described. It was observed that except in the case of the cyclopropyl ketone 106, where both the nitriles were found to react with the double bond keeping the cyclopropane ring intact, in all the other cases the cyclopropane ring was opened with concomitant attack of nitrile leading to the formation of the Ritter reaction products N-(β-phenacylphenethyl)amides 111 & 112 from the cyclopropyl ketone 105 and N-homoallyl amides from the cyclopropyl carbinols 107, 108 & 109.

Chapter II, which has been divided into two parts A & B, deals with two reagent systems that have been utilised for carrying out a number of useful functional group transformations. In part A, sodium iodide-boron trifluoride etherate ($NaI-BF_3.Et_2O$) has been shown to be an extremely versatile reagent system for affecting four different transformations, viz. (i) conversion of

allylic and benzylic alcohols into iodies, (ii) selective cleavage of benzyl ethers, (iii) reduction of sulphoxides to sulphides and (iv) reduction of conjugated ene-diones. A study of each of these is presented in a separate section, giving in the beginning of the section, a brief background of the various reagent systems available in the literature for affecting that particular transformation.

Using NaI-BF_3.Et_2O, a number of allylic alcohols 13, 15, 17 & 18 and a number of benzylic alcohols 32-37 have been converted to their corresponding iodides under extremely mild conditions, in yields ranging from 74-95%. In case of allylic alcohols, the iodides were formed regioselectively without allylic rearrangement. Further, the high selectivity of the NaI-BF_3.Et_2O reagent system towards allylic and benzylic alcohols was evident from the reaction with 2-(m-hydroxymethylphenoxy)ethanol (38) and 5-hydroxyhept-6-en-1-ol (30), which gave exclusively their corresponding mono-benzylic and allylic iodides 46 and 31 without affecting the primary hydroxyl group.

A number of alkyl benzyl ethers 53-55 & 59, and aryl benzyl ethers 61 & 62 were shown to be cleaved, under mild conditions, to their corresponding alcohols in 74-94% yields, using the NaI-BF_3.Et_2O reagent system. Once again this reagent was shown to be selective as itwas apparent from the rate of reactivity, as well from the examples 65, 67 & 69, where only the benzylic ether was cleaved in preference to other ethers such as aliphatic methyl and phenolic methyl ethers. It was

evident from the reaction times for cleavage of various ethers, that the rate of cleavage of benzylic ether group was much higher compared to other ethers, the order being benzylic > aliphatic methyl> aryl methyl ethers.

Reduction of both aryl and alkyl sulphoxides to sulphides with NaI-BF_3.Et_2O has been shown to be extremely mild and high yielding. Functional groups like, -CN, -CO_2Me and -OCH_3 were found to be unaffected under the reaction conditions, as evidenced by examples 93-95.

It was found that the NaI-BF_3.Et_2O reagent system reduces the double bond of a variety of conjugated ene-dicarbonyl compounds 130-135 in a facile manner, in yields ranging from 88-99% under extremely mild conditions, as compared to the existing literature methods. A rationale for the success of this reaction has been discussed.

In part B of Chapter II, two different reduction reactions viz. (i) reduction of oxiranes and (ii) reduction of conjugated ene-diones, that have been carried out using zinc-chlorotrimethylsilane (Zn-$ClSiMe_3$) reagent system, are described in two separate sections. Using Zn-$ClSiMe_3$ a variety of oxiranes were reduced in an extremely facile manner in 80-96% yields to the corresponding alcohols. In case of unsymmetrical epoxides 174-176, it was found that this reagent is regioselectively giving the less substituted alcohols in major amounts. Further, reduction of 2,3-epoxy ketals 203a-c & 207 was found to be highly

regioselective. Thus, epoxy ketals 203a, 203b & 207, obtained from cyclohexanone, 2-methyl cyclohexanone and cycloheptanone, respectively gave the 2-hydroxy ketals, whereas 203c, obtained from 4-methyl cyclohexanone, gave only the 3-hydroxy ketal probably due to steric factors. However, no regioselectivity was observed with epoxyacetates 217-220, although the ester group was unaffected under the reaction conditions.

The reagent system Zn-$ClSiMe_3$ was also shown to reduce the double bond of conjugated ene-diones 130-134 to give 1,4-diketones. This method was, however, found to be unsuitable for the reduction of ene-diester 135. A probable mechanism for the reduction of ene-diones with this reagent system has been described. The NaI-$BF_3.Et_2O$ and the Zn-$ClSiMe_3$ reagent systems should provide convenient alternative to the other existing systems reported in literature, for affecting the various transformations described, because of their mildness, facility and selectivity.

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CHAPTER I

SOME NEWER ASPECTS OF RITTER REACTION

I.1 Introduction

Addition of nitriles to olefins in the presence of concentrated sulphuric acid to form N-substituted amides was first reported by Ritter[1] in 1948 and is known as the "Ritter Reaction". This reaction has since been extended to a wide variety of compounds capable of generating carbenium ions and has emerged as an important synthetic reaction.[2-4]

In its most general form, the Ritter reaction involves addition of a nitrile to a carbenium ion generated in the presence of conc. sulphuric acid, to give an adduct **1**, which is subsequently hydrolysed by water to form the amide. The mechanism[1,5] for the reaction between isobutene and acetonitrile is illustrated in Scheme I.1:

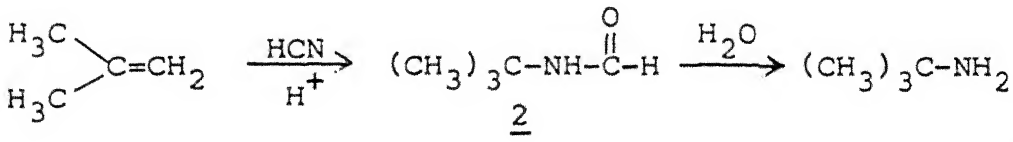
$$(CH_3)_2C{=}CH_2 + H_2SO_4 \rightleftharpoons (CH_3)_3C^+ + HSO_4^-$$

$$(CH_3)_3C^+ + N{\equiv}C{-}CH_3 \longrightarrow (CH_3)_3C{-}\overset{+}{N}{\equiv}C{-}CH_3 \xrightarrow{HSO_4^-} \underset{\mathbf{1}}{(CH_3)_3C{-}N{=}C(OSO_3H){-}CH_3}$$

$$\xrightarrow{H_2O} (CH_3)_3C{-}NH{-}CO{-}CH_3$$

SCHEME I.1

When HCN is employed as the nitrile component the resulting N-alkylformamide 2 can be readily hydrolysed to the corresponding carbinamine (Eqn. I.1). The above mechanism is amply



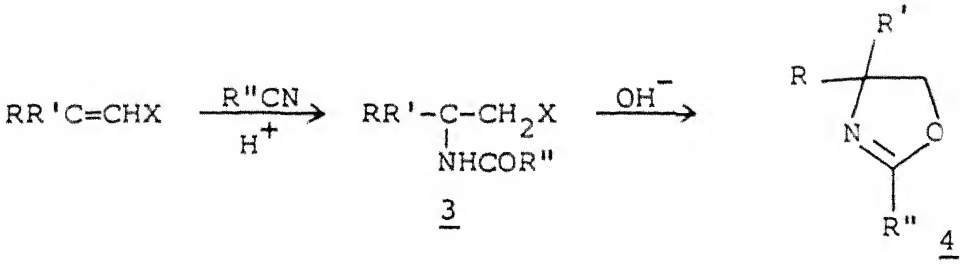
..(I.1)

supported by experimental facts.[6,7]

A variety of compounds, besides alkenes, can serve as a source of carbenium ion.[4] These include alkanes, alkadienes, simple and spiro alcohols, alkyl halides, aldehydes, glycols, chlorohydrins, N-methylolamides, ethers, carboxylic acids, esters, ketones, ketoximes etc. Besides simple nitriles and HCN, cyanohydrins, cyano acids (or esters), and other substituted nitriles have also been used for the Ritter reaction. Several other acids (besides sulphuric acid) such as perchloric acid,[8] phosphoric acid,[9] formic acid,[10] substituted sulphonic acids[11] and Lewis acids like boron trifluoride,[12] stannic chloride[13] etc. have also been used for the generation of carbenium ions.

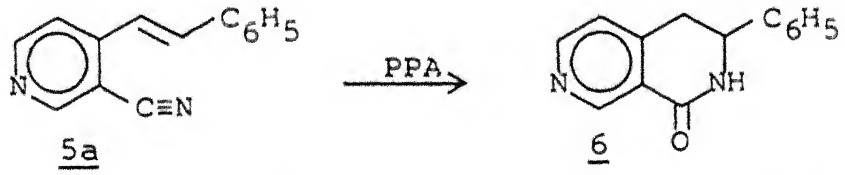
The Ritter reaction has been utilized in the synthesis of several interesting and useful heterocyclic compounds,[4] in addition to the simple amination reactions. Haloalkenes of the type $R_2C{=}CHX$, react with nitriles to give N-(2-halo-1-ethyl)amides 3 in good yields. The haloamides can be

cyclized by base to give oxazoline 4 [14] (Scheme I.2):



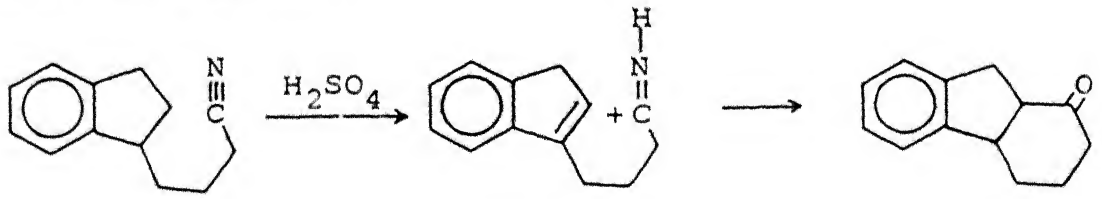
SCHEME I.2

Nitriles can add on to carbenium ions in an intramolecular fashion, provided the nitrile function is suitably located for the cyclization. Bobbitt and Doolittle[15] were able to successfully cyclize 3-cyano-4-stilbazole (5a) to the lactam 6 in good yields, using polyphosphoric acid (PPA) (Eqn. I.2).



..(I.2)

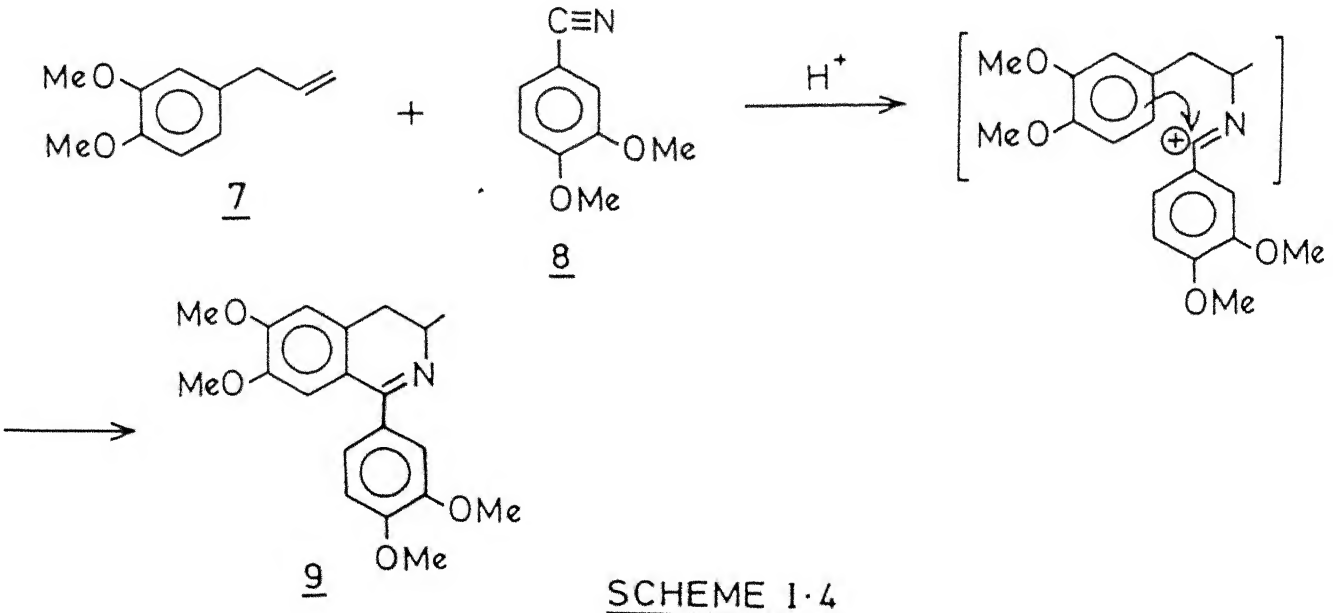
However, in case of γ,3-indenylbutyronitrile (5b),[16] cyclization with sulphuric acid led to the attack of olefin on protonated nitrile instead of intramolecular Ritter reaction, probably due to entropically unfavourable situation for nitrile attack (Scheme I.3):



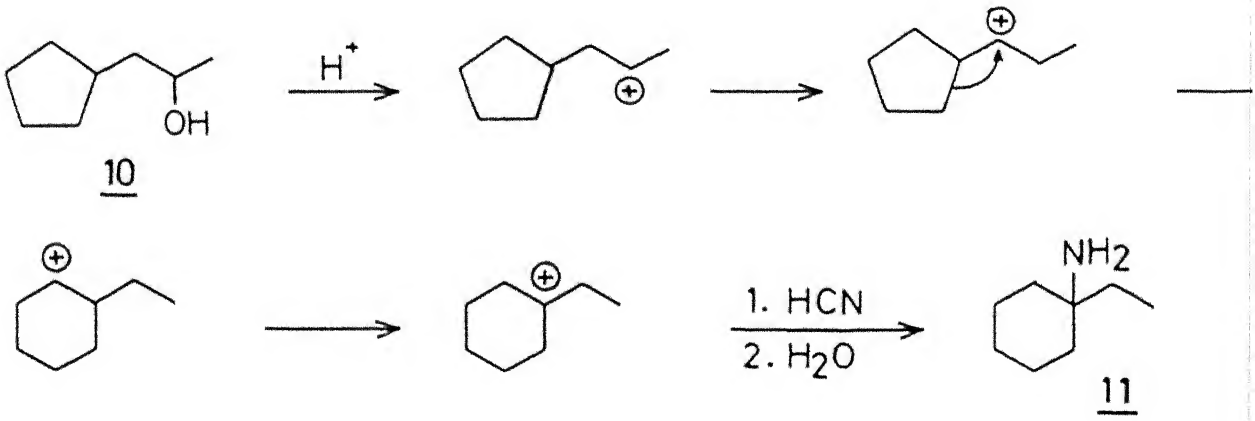
5b

SCHEME I.3

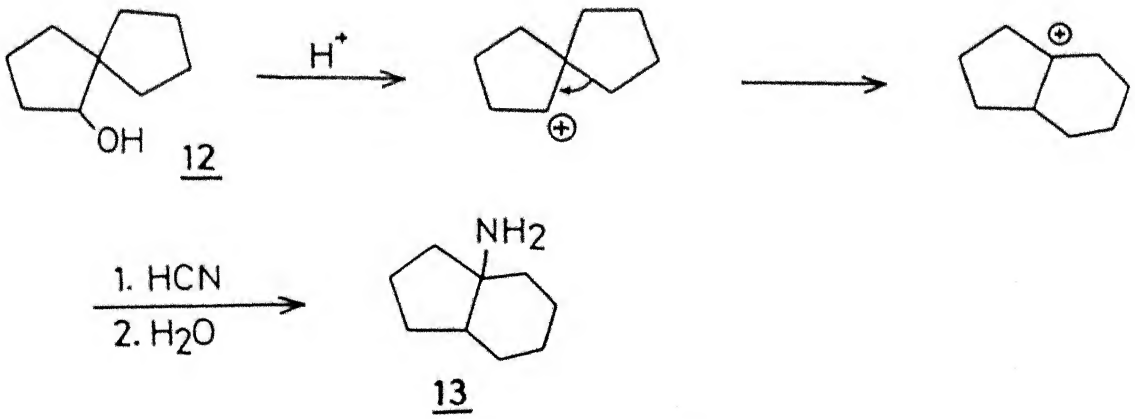
Nitrilium ions, generated by intermolecular attack of nitrile can cyclize with a suitably located electron rich



SCHEME 1·4



SCHEME 1·5

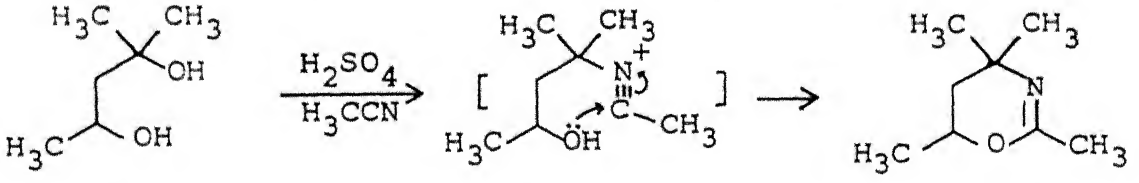


SCHEME 1·6

aryl ring to give 3,4-dihydroisoquinolines. Thus, veratronitrile (7) and methyeugenol (8) gave the dihydroisoquinoline derivative 9 ,[17] (Scheme I.4).

Simple primary alcohols fail to undergo Ritter reaction even at elevated temperatures, however, aralkyl alcohols react smoothly with nitriles. The initially formed carbenium ions from alcohols by an acid, may rearrange to more stable carbenium ions before the attack of nitrile. Thus, 3-cyclopentyl-2-propanol (10) underwent a series of prototropic shifts, before attack by HCN to give, 1-ethylcyclohexylamine (11) as the major product[18] (Scheme I.5). Interestingly, spiro alcohols are found to undergo Ritter reactions with the accompaniment of retropinacol rearrangement. Thus, spiro[4,4]-1-nonanol (12) gave the aminohydrindane 13 with HCN,[19] (Scheme I.6).

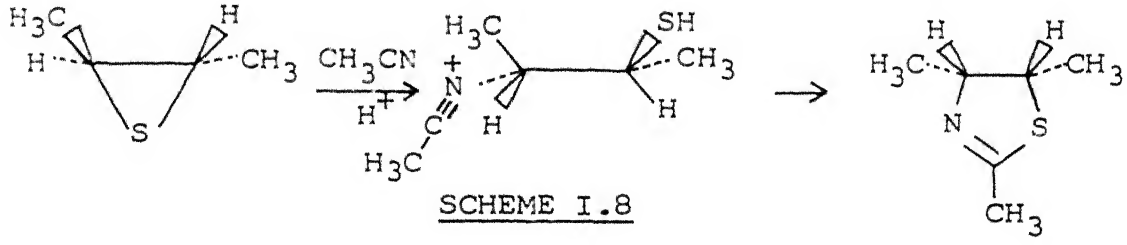
Ritter and Tillmanns[20] have found that interaction of a suitably substituted diol with a nitrile results in the formation of a dihydro-1,3-oxazine, instead of the expected diamide. Thus, when 2-methyl-2,4-pentanediol (14) was treated with acetonitrile the 1,3-oxazine 15 was obtained (Scheme I.7)



14 SCHEME I.7 15

by preferential attack of nitrile on the more stable tertiary cation followed by cyclization of the resulting nitrilium ion by the secondary hydroxyl group.

Δ^2-Thiazolines have been synthesized in a stereospecific manner from episulphides[21,22] as illustrated in Scheme I.8.

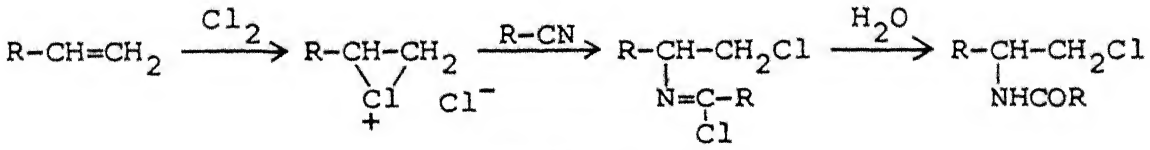


SCHEME I.8

The mechanism involves nucleophilic attack of a nitrile on the incipient carbenium ion generated from protonated episulphide, followed by ring closure, to form the thiazoline.

Several other heterocyclic systems such as thiazines, pyrrolines, pyridones, triazines etc. have been synthesized[4] by both intermolecular as well as intramolecular attack of nitriles on carbocations generated by the action of strong mineral acids.

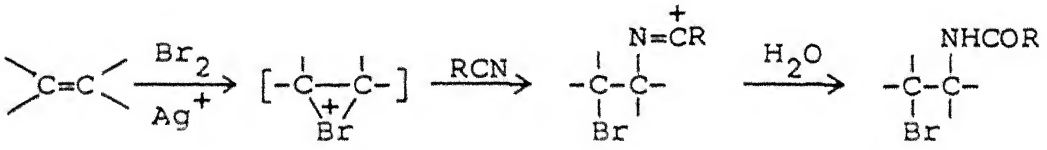
The scope of Ritter reaction has been considerably extended by nitrile trapping of incipient carbenium ions generated from reactions which obviate the use of strong acids. Cairns and coworkers[23] have demonstrated the formation of imidoyl chloride, produced in the reaction of chlorine with an olefin in the presence of an alkyl/aryl nitrile, which could be readily hydrolyzed to an N-(2-chloroalkyl)amide (Scheme I.9):



SCHEME I.9

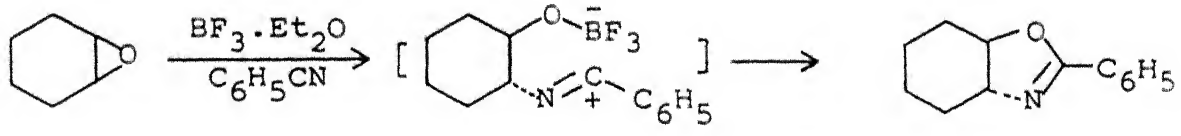
The reaction obviously involves the attack of a nitrile on

halonium ion intermediate. Hypochlorous acid[24] and sulphuryl chloride[25] have also been used as a source of chloronium ion. Likewise, bromine has also been used to generate incipient carbenium ions. In this case a nitrile opens the intermediate cyclic bromonium ion in a stereospecific manner. The reaction proceeds only when the halide anion liberated from the original halogen is removed from solution (by use of a silver salt) (Scheme I.10):



SCHEME I.10

Lewis acids have also been successfully used to generate incipient carbenium ions for Ritter reaction. Norman et al.[26] have stereospecifically synthesized dihydro 1,3-oxazolones, by a nitrile attack on incipient carbenium ions generated from oxiranes by the action of boron trifluoride. An example with cyclohexene oxide is shown in Scheme I.11.



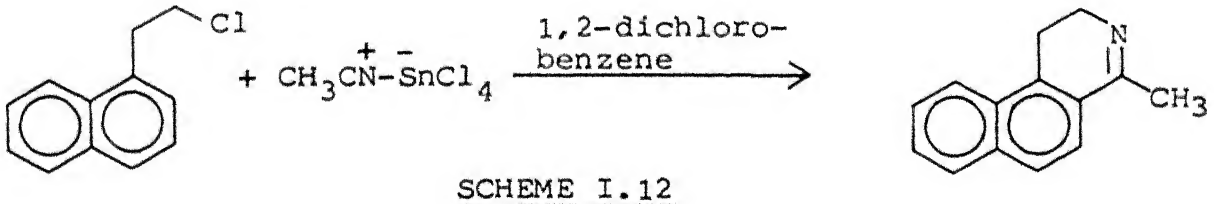
SCHEME I.11

Recently, Pavel[27] has extended this reaction to 1,3-epoxides (oxetanes) to give dihydro 1,3-oxazines.

Episulphonium salts, generated from alkyl sulphinyl chloride and olefins, in presence of silver tetrafluoroborate,

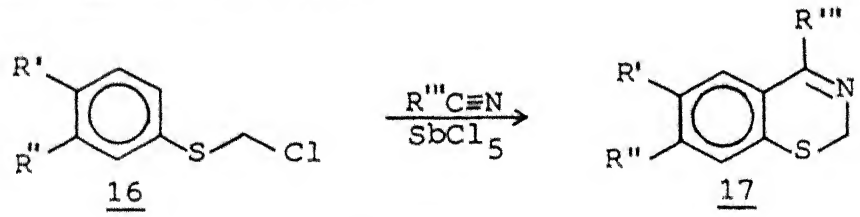
have been shown to be attacked by nitriles to give β-mercaptoalkyl amides.[28] Likewise aminoselenation of olefins has been achieved with phenylselenyl chloride and nitriles in the presence of an acid catalyst.[29]

Although primary alcohols do not react under Ritter reaction conditions, primary halides react with nitrilium salts[13] derived from a Lewis acid and a nitrile (Scheme I.12). This is probably because the incipient carbenium ion generated in this case, in a non-nucleophilic medium, has sufficient activation to be attacked by a nitrile. Thakur and Vankar[30]



SCHEME I.12

have recently extended this reaction to chloromethylphenylsulphides 16 (using nitrilium salts derived from $SbCl_5$ and nitriles) to obtain pharmacologically active 2H-benzothiazines 17 (Eqn. I.3):

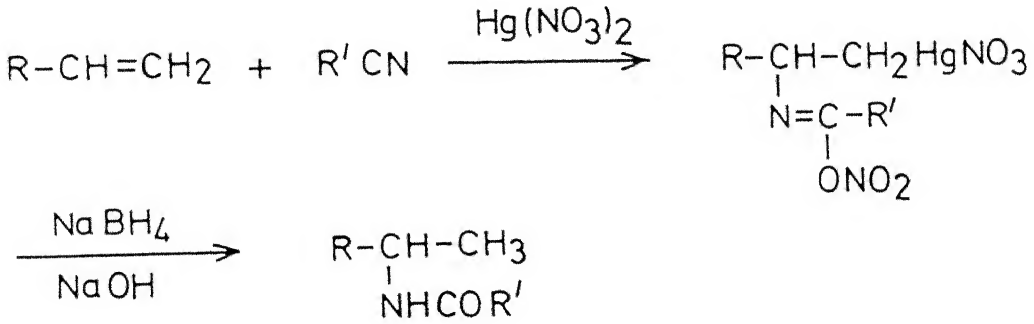


..(I.3)

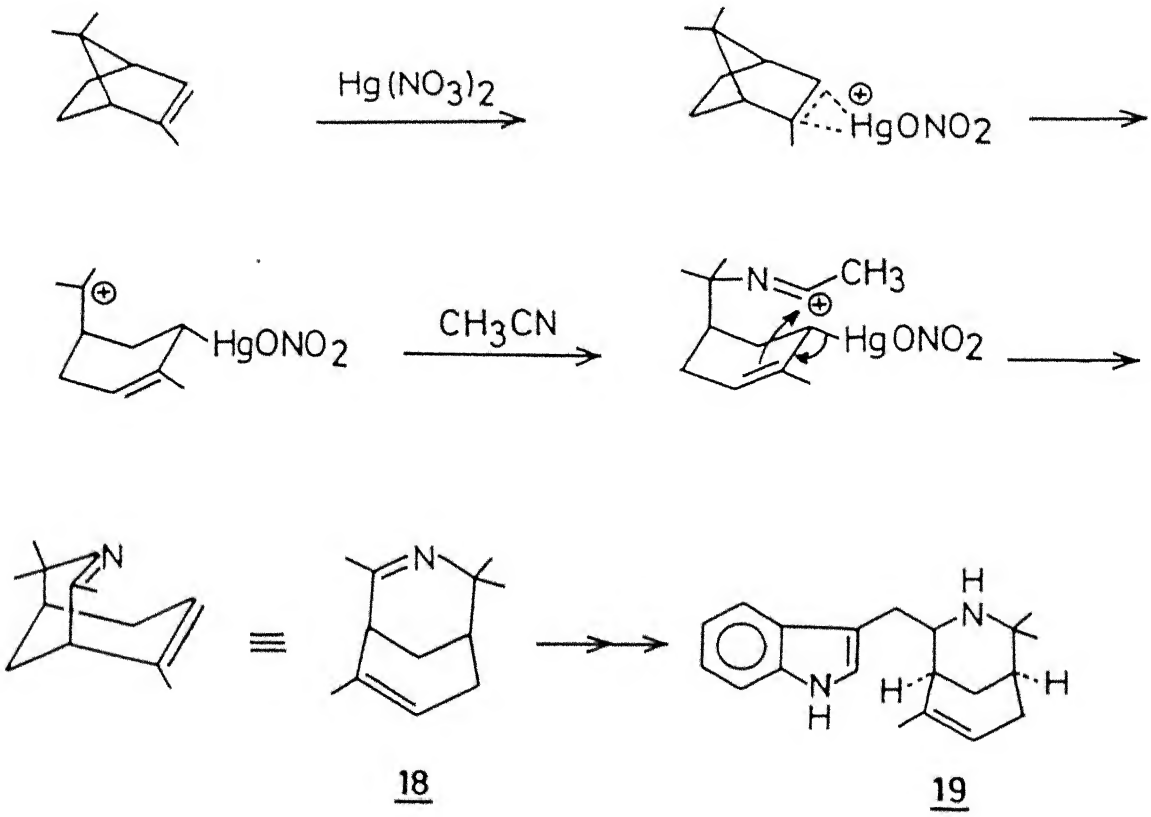
Brown and Kurek[31] have shown that the incipient carbenium ions generated from olefins in the presence of mercuric nitrate, add to nitriles, and after treatment with sodium borohydride, give the same amides which would be obtained by

the classical Ritter reaction (Scheme I.13). This method provides a convenient alternative to the classical Ritter reaction, as it obviates the use of strong acids. This reaction has recently been used in the synthesis of the key intermediate 19 , for the total synthesis of the alkaloid hobartine 20 ,[32] starting from α-pinene. The reaction sequence is illustrated in Scheme I.14.

In the present work, the Ritter reaction on two different kinds of carbocationic intermediates has been investigated and these studies are presented in two parts, viz., Part A: Ritter Reaction on carbocationic intermediates generated in Pummerer rearrangement and Part B: Ritter reaction on carbocationic intermediates generated from cyclopropyl ketones and carbinols.



SCHEME I·13



18 19

SCHEME I·14

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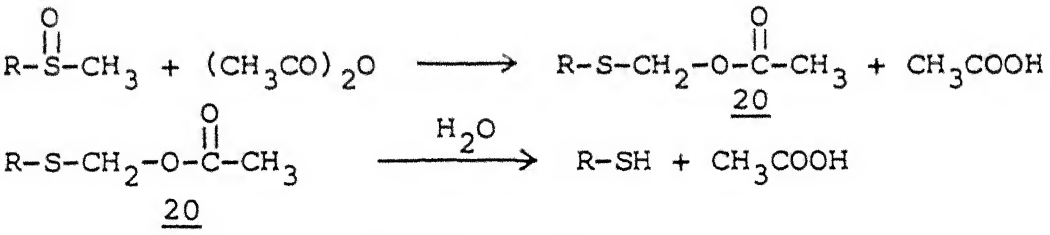
PART- A: RITTER REACTION ON PUMMERER INTERMEDIATE

I.A.1 Background

Sulphoxides bearing at least one α-hydrogen atom readily react with acylating agents resulting in the formation of α-acyloxy sulphides.[1,2] This interesting reaction of sulphoxides, known as the "Pummerer Rearrangement," has been well studied[3] and is finding increasing application in organic synthesis.[4] In cases, for example, when acetic anhydride is reacted with a sulphoxide, an α-acetoxy sulphide 20 is formed which readily hydrolyses in aqueous medium to the corresponding thiol as formulated in Scheme I.15:

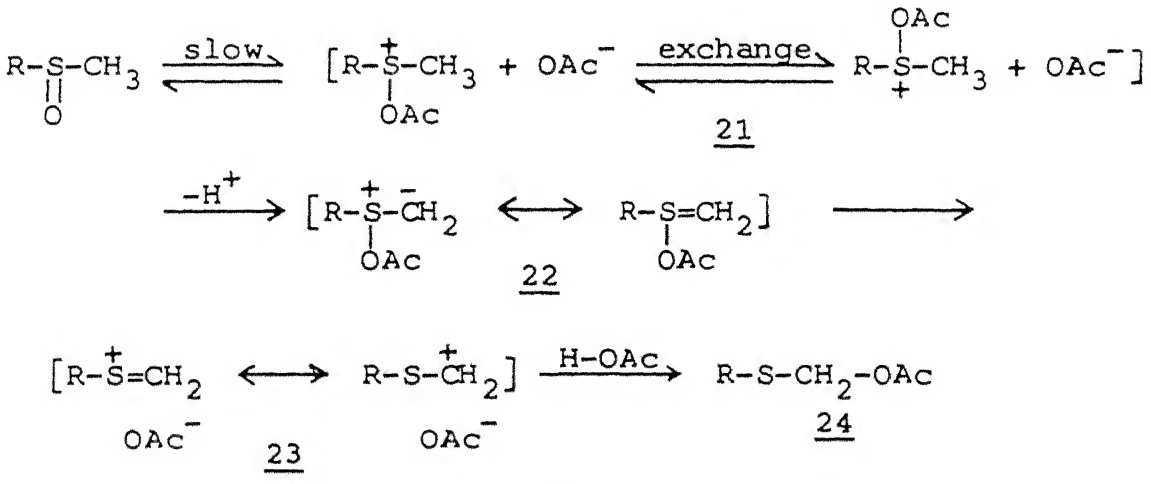


SCHEME I.15

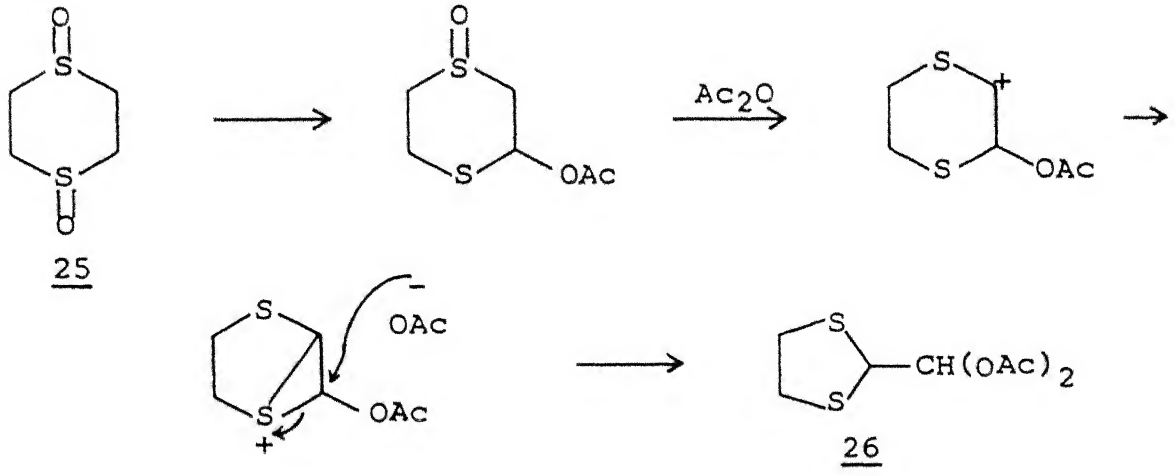
Bordwell and Pitt have suggested[5] that the Pummerer rearrangement proceeds through the intermediacy of an acyloxysulphonium salt 21 , which is converted to an ylid 22 , followed by its disproportionation to give a resonance stabilized sulphenium ion 23 . Intermolecular nucleophilic attack of the acetoxy group on the methylene carbon of 23 gives the α-acetoxy sulphide 24 (Scheme I.16).

The formation of gem-diacetate 26 from the bissulphoxide 25 provides evidence[6] for the carbocationic intermediate of

type 23 in the Pummerer rearrangement (Scheme I.17).

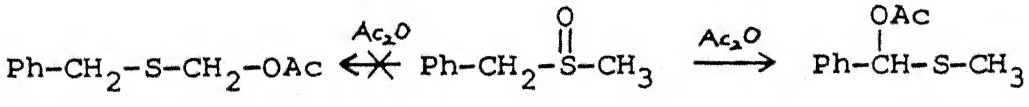


SCHEME I.16



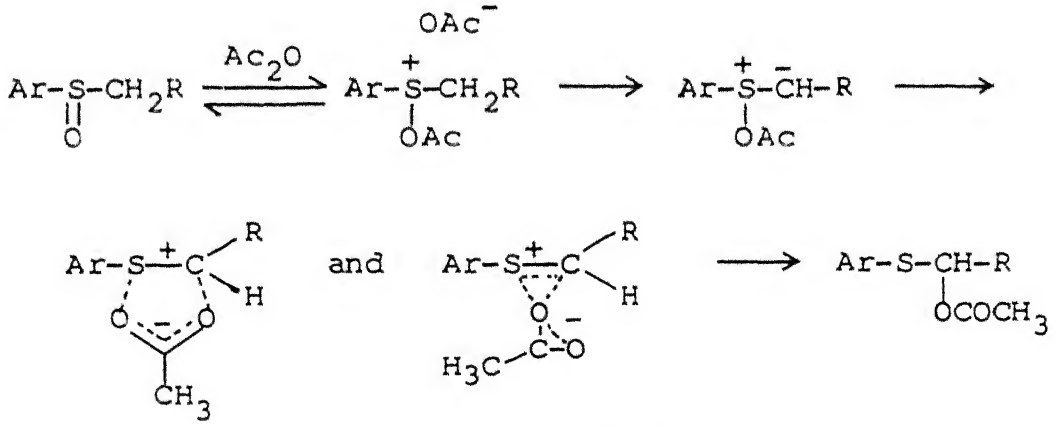
SCHEME I.17

The migration of acyloxy group to the site of more acidic α-hydrogen in the case of Pummerer rearrangement with unsymmetrical sulphoxides (Scheme I.18) also supports[7-9] this mechanism.



SCHEME I.18

The mechanism of Pummerer rearrangement may vary markedly with subtle changes in the structure of the starting sulphoxide and with changes in reaction conditions. This has been proved through an interesting study by Itoh et al.,[10] (based on stereochemical changes on α-carbon, and isotopic retention studies with ^{18}O labelled sulphoxides) who have shown that the nucleophilic attack of acetoxy group on the methylene carbon of 23 varies from an intermolecular attack to an intramolecular acetoxy migration (Scheme I.19) depending upon the nature of the substituent at α-carbon. Thus, when R = CN, intramolecular

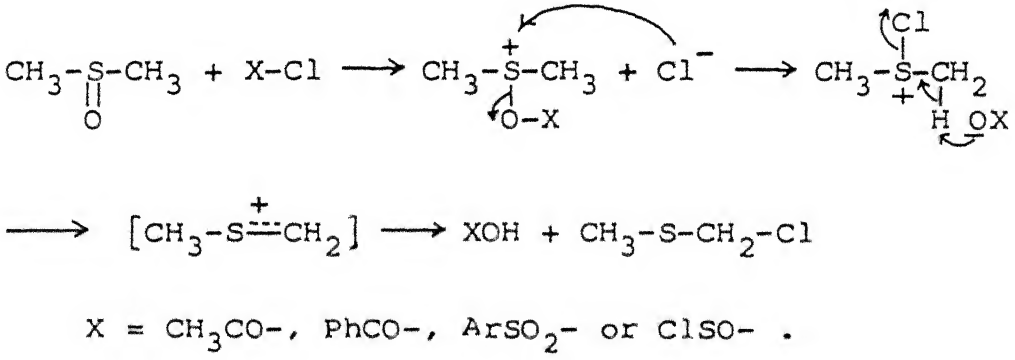


SCHEME I.19

acetoxyl migration appeared to be favoured and when R = $-C_6H_5$, intermolecular attack of acetate seems to be preferred.[10] However, this study has not been conducted with other type of substituents at the α-carbon.

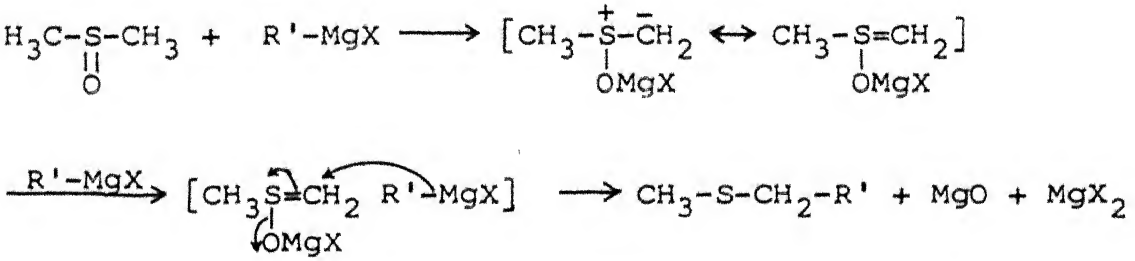
A variety of electrophilic reagents have been utilized in carrying out Pummerer rearrangement. These include reagents like trifluoroacetic anhydride,[11] dicyclohexyl carbodiimide,[12] acid chlorides,[13] mineral acids,[14] p-toluenesulphonic acid,[15]

aryl sulphonyl chlorides,[16] thionyl chloride[5] etc. Acid chlorides, sulphonyl chloride and thionyl chloride all lead to the formation of α-chloromethyl sulphide upon reaction with dimethyl sulphoxide (Scheme I.20). Other sulphoxides also undergo similar reaction.



SCHEME I.20

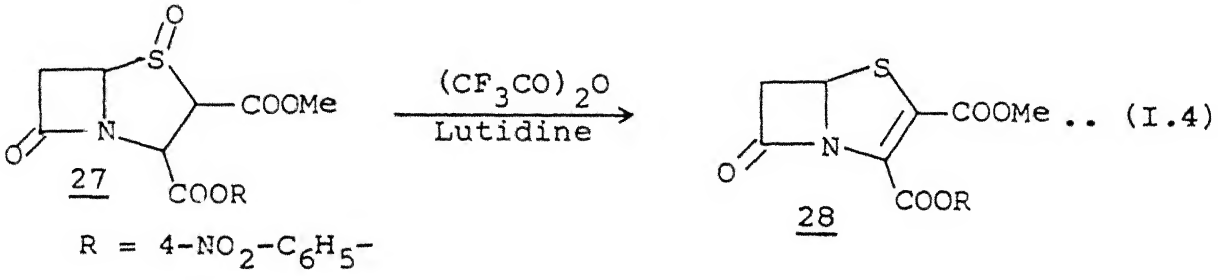
Interestingly, even Grignard reagents react with dimethyl sulphoxide to give compounds possessing a general formula CH_3-S-CH_2-R',[17] the formation of which is rationalised schematically as given below (Scheme I.21):



SCHEME I.21

The Pummerer rearrangement has been applied to a variety of sulphoxide systems and many interesting features have been noted. For example, cyclic sulphoxides under Pummerer rearrange-

ment conditions give the corresponding cyclic olefinic sulphides.[6] Recently, this aspect has been utilised in the synthesis of the pinem 28 from the sulphoxide 27 [18] (Eqn. I.4):



.. (I.4)

The examples shown above illustrate the intermolecular attack of nucleophiles (which are generated from the electrophilic reagent itself) on the Pummerer intermediate, i.e. $[R\text{-}S\text{-}\overset{+}{C}H_2 \leftrightarrow R\text{-}\overset{+}{S}{=}CH_2]$. However, recently a number of cases have been studied in which the highly reactive Pummerer intermediates from β-ketosulphoxides have been trapped in an intramolecular fashion by a variety of suitably located electron rich moieties such as an aromatic ring, a double bond or an enamine. These reactions are of considerable synthetic importance in forming carbocyclic rings.

Oikawa and Yonemitsu[19] were the first to demonstrate an intramolecular attack of the aromatic ring on the intermediate α-thiocarbocation 30 derived from the reaction of the β-ketosulphoxide 29 , with acids such as p-toluenesulphonic acid or trifluoroacetic acid (Scheme I.22, page 19).

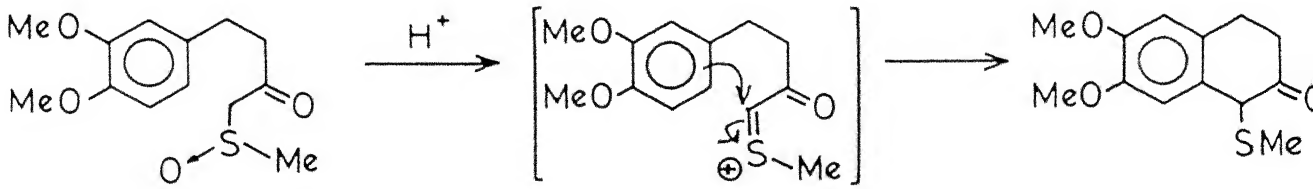
A remarkable application of Pummerer rearrangement in the synthesis of the indole alkaloid Aspidospermidine (33) has been recently reported by Magnus et al.,[20] which proceeds

through an intramolecular cyclisation of the enamine system on the Pummerer intermediate 32 generated from the sulphoxide 31 as illustrated in Scheme I.23.

The reactive Pummerer intermediates can also act as highly reactive initiating centres for intramolecular cation-olefin cyclisations.[21-23] Recently Tamura et al. have demonstrated that N-2-alkenyl-N-methyl-α-(methylsulphinyl)acetamides could be cyclised to six and five membered lactams under Pummerer rearrangement conditions.[24] The cation-π cyclisations by Pummerer rearrangement of β-ketosulphoxides can provide useful alternative to the related diazoketone process,[22] as illustrated in Scheme I.24.

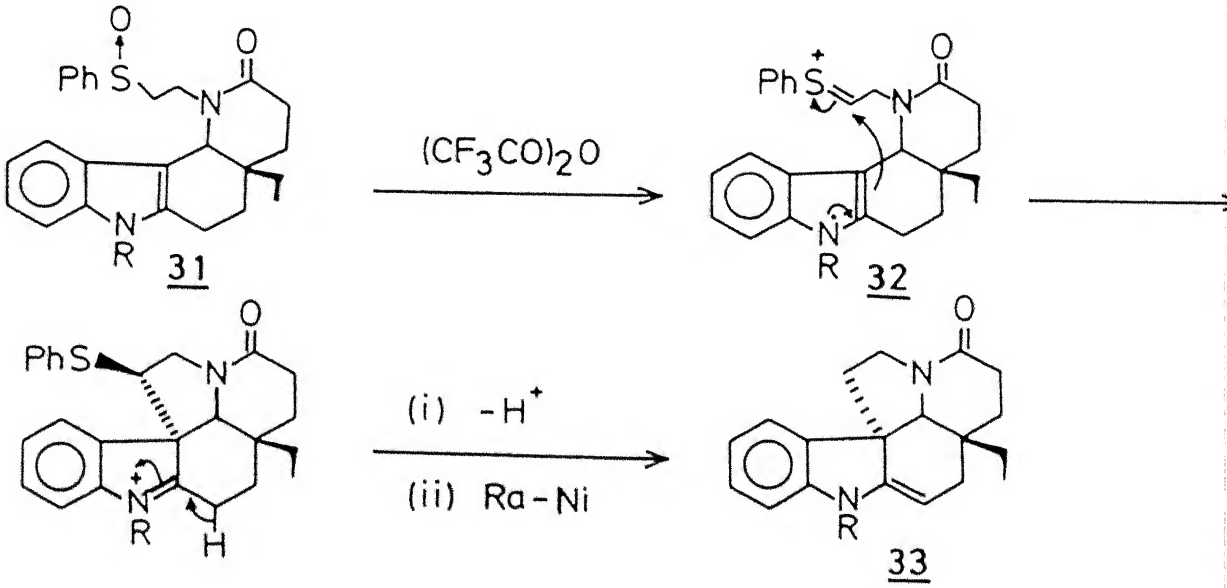
Further aspects of the Pummerer rearrangement, in which nucleophiles, which are not part of the electrophilic reagent, attack the Pummerer intermediate in an intermolecular fashion have recently been demonstrated. For example, the α-thiocarbocation generated from the sulphoxide (34) is capable of intermolecular electrophilic substitution with various aromatic hydrocarbons[25-27] (Scheme I.25, page 20).

Olefins (especially 1-alkenes) have also been shown to be potential nucleophiles which can attack the Pummerer intermediate intermolecularly, giving ene adducts.[28] This novel "ene reaction" ($\sigma^2 + \pi^2 + \pi^2$) provides a new convenient route for the synthesis of E,E-2,4-alkadienoic esters 36 via oxidative desulphurisation of the adduct 35 [29] (Scheme I.26).



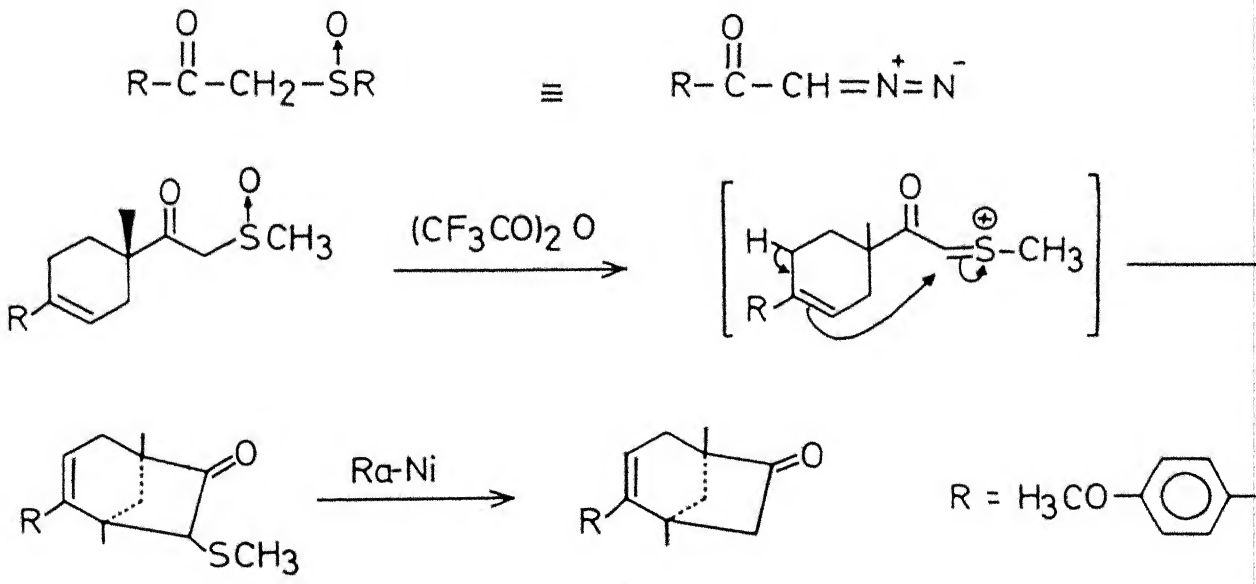
29 30

SCHEME I·22

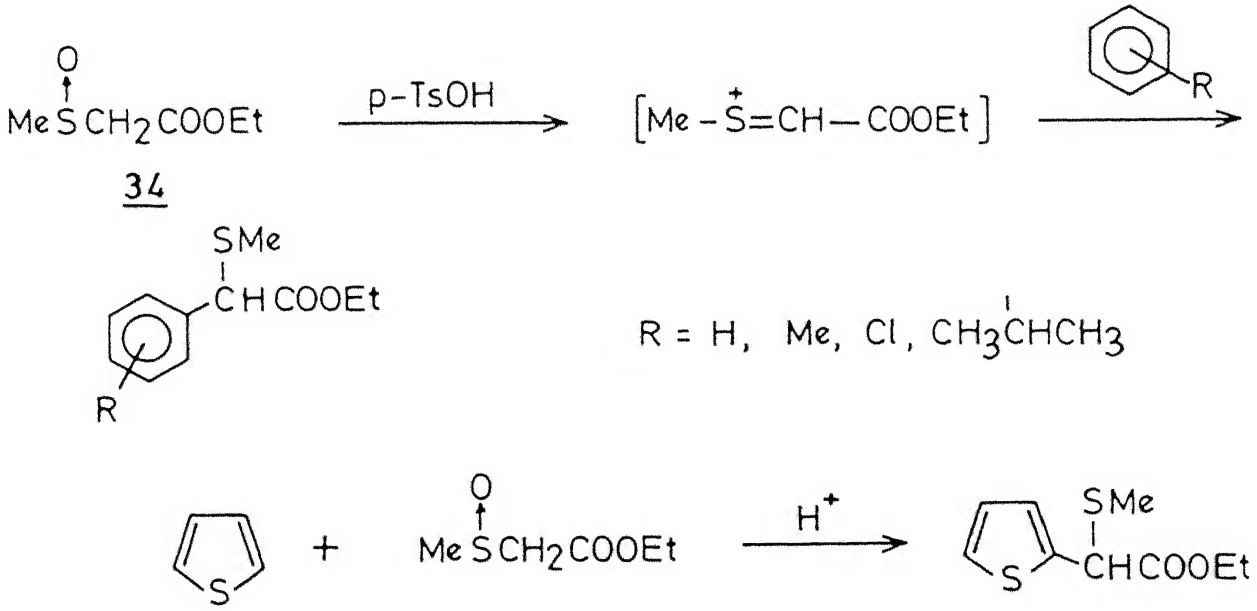


31 32 33

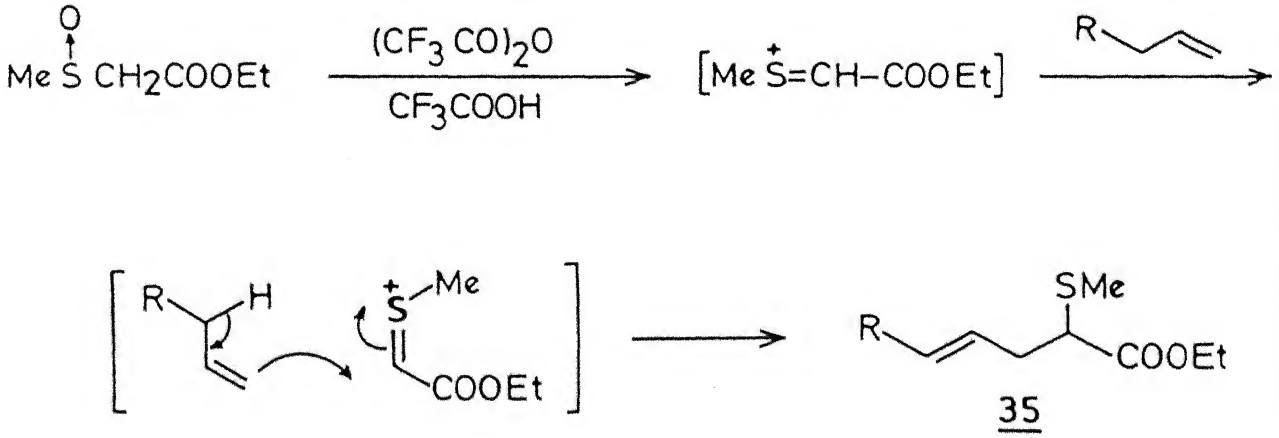
SCHEME I·23



SCHEME I·24



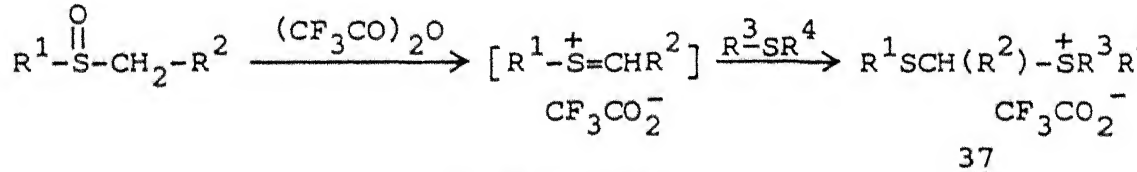
SCHEME I·25



SCHEME I·26

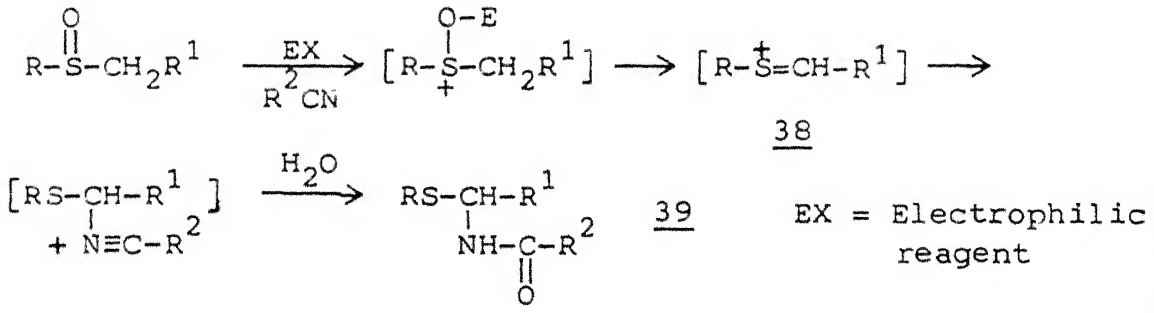
I.A.2 Present Work

From the literature survey on the Pummerer rearrangement described in the background part of this chapter, it is clear that a large number of nucleophiles have been added to the Pummerer intermediates and the products isolated and further used in organic synthesis. In most cases the anionic portion of the electrophile used acted as a nucleophile, except in intramolecular cases where a suitably located electron rich centre in the molecule acted as a nucleophile. Nucleophiles different from the above described ones have also added in an intermolecular fashion, and some examples of such type are illustrated towards the end of the background part. These nucleophiles include aromatic rings and olefins. Recently, however, one report from Tanikaga et al.[30] has appeared, where dimethyl sulphide has been utilised to trap the Pummerer intermediate giving a dimethylsulphonium salt 37 (Scheme I.27).



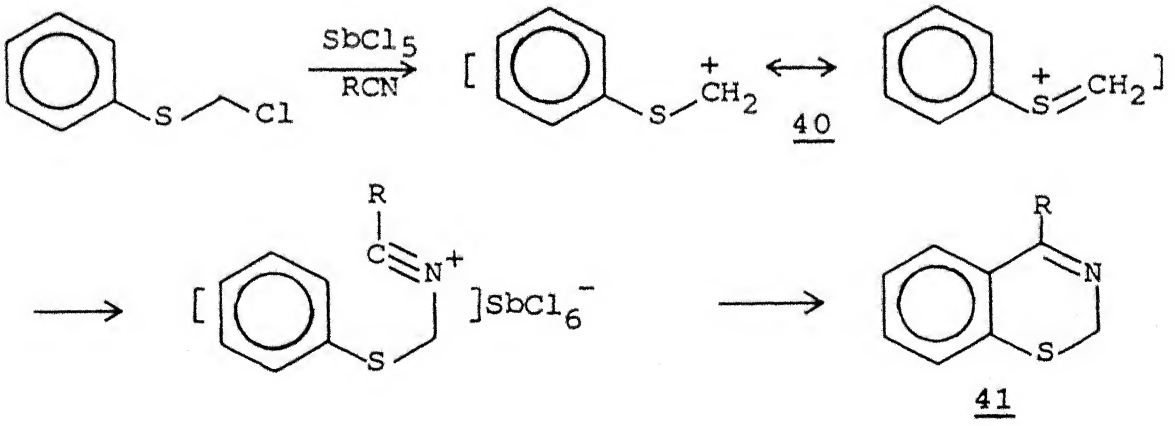
SCHEME I.27

In the present work, we have undertaken a study, wherein nitriles have been used as nucleophiles to trap the Pummerer intermediates 38 , thereby producing the corresponding amides 39 A general scheme is represented below (Scheme I.28)



SCHEME I.28

This way of synthesizing amides is analogous to Ritter reaction except that the carbenium ion produced here is not in a conventional Ritter reaction manner. To our knowledge, this appears to be the first report of Ritter reaction on Pummerer intermediate, which is generated from a sulphoxide. An earlier report[31] from our laboratory has recently appeared in the literature where 2H-benzothiazine derivatives have been synthesized starting from chloromethyl arylsulphide and nitrile in the presence of $SbCl_5$ (Scheme I.29). In these cases, a variety of examples that have been studied conformed the generality of the reaction. It was presumed that the reaction involved the formation of an intermediate 40.



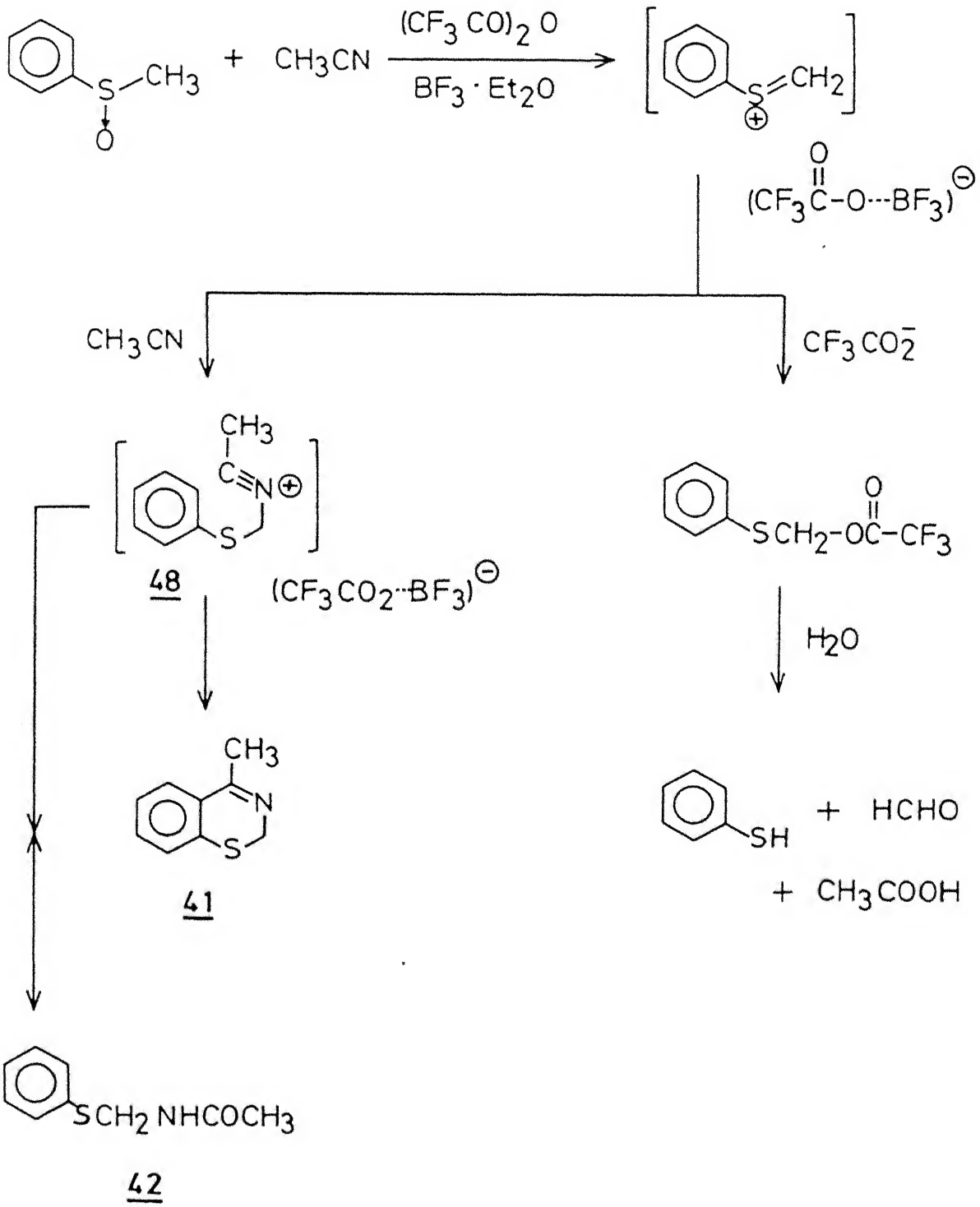
SCHEME I.29

This also appeared to be the first report wherein a carbenium ion generated α to a sulphur atom is trapped by a nitrile.

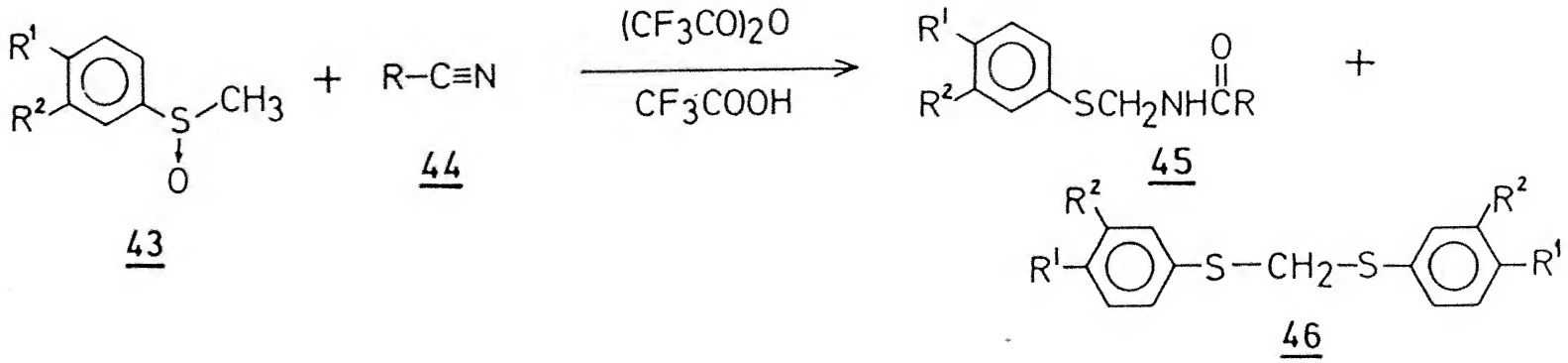
The structural similarity of the intermediate 40, with that of the Pummerer intermediate was another factor that prompted us to undertake the present study, with a view to explore the possibility of synthesizing 2H-benzothiazine derivatives from sulphoxides. As it is well known that Pummerer rearrangement does proceed via sulphenium ion [$R\text{-}\overset{+}{S}{=}CH_2 \leftrightarrow R\text{-}S\text{-}\overset{+}{C}H_2$], our study would further confirm the intermediacy of such intermediates.

In the present study, we chose a number of sulphoxides and three nitrles which are listed in Scheme I.30. The electrophiles (and electrophilic systems) used by us include $(CF_3CO)_2O$, $(CF_3CO)_2O/BF_3.Et_2O$ and $(CF_3CO)_2O/CF_3COOH$

Trifluoroacetic anhdride (TFAA) was the first electrophilic reagent used in our study. We expected the reaction of a sulphoxide with TFAA in an excess of a nitrile to lead to the formation of 2H-benzothiazine derivative 41 and/or the amide 42 by trapping of the Pummerer intermediate by the nitrile under study (Scheme I.30). In view of the fact that trifluoroacetate ion is a weak nucleophile, and a large excess of nitrile was used in the reaction, we expected the nitrile rather than the trifluoroacetate anion to attack the Pummerer intermediate. However, when thioanisole sulphoxide was treated with 1.5 molar equivalents of TFAA in dry acetonitrile at $0^{\circ}C$, a fast reaction (30 min.) was observed to take place as indicated by the


(CF3 CO)2 O
BF3 · Et2O
CH3CN
CH3
S
O
CH2
(CF3C-O···BF3)⊖
CH3CN
CF3CO2⁻
CH3
C≡N⊕
S
48
(CF3CO2···BF3)⊖
SCH2-OC-CF3
H2O
CH3
N
S
41
SH
+ HCHO
+ CH3COOH
SCH2 NHCOCH3
42

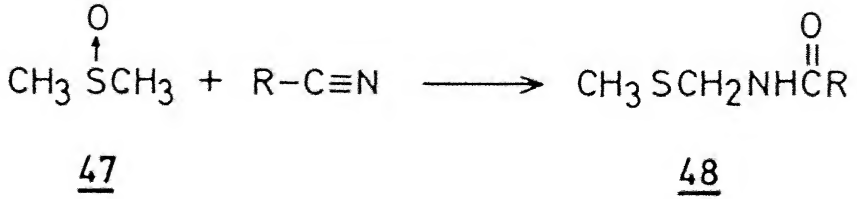
SCHEME I·30



R = CH_3 : a R^1 = H, R^2 = H; b R^1 = CH_3, R^2 = H; c R^1 = H, R^2 = OCH_3

R = $CH=CH_2$: d R^1 = H, R^2 = H; e R^1 = CH_3, R^2 = H

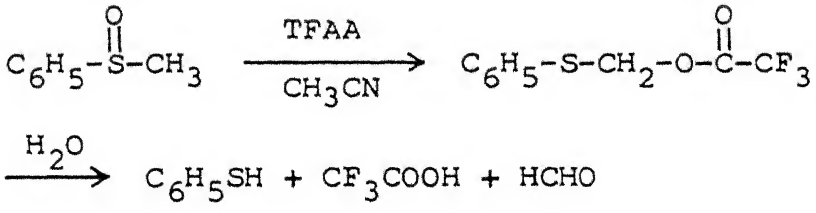
R = Ph : f R^1 = H, R^2 = H; g R^1 = CH_3, R^2 = H



h R = CH_3
i R = $CH=CH_2$
j R = Ph

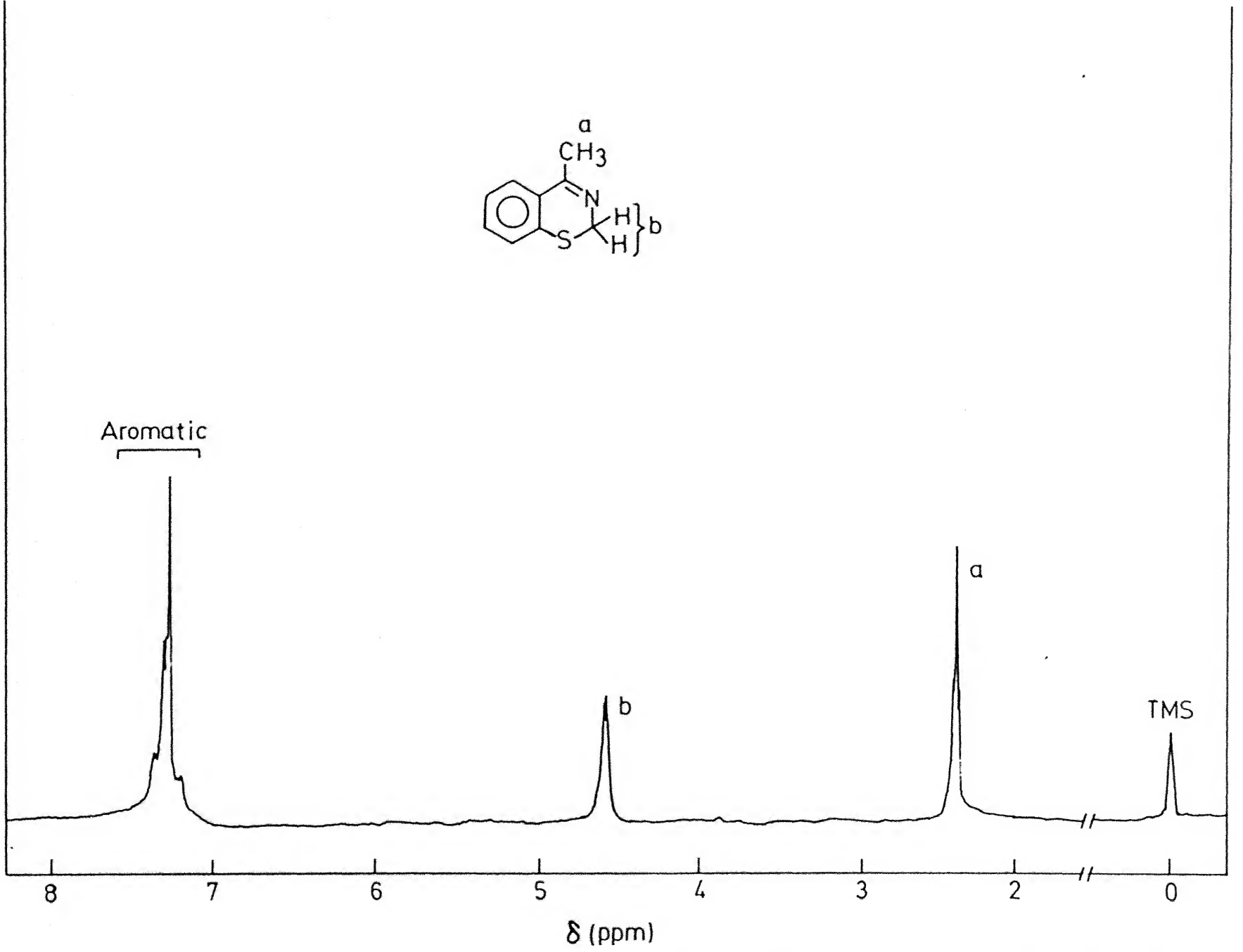
SCHEME I·31

disappearance of the sulphoxide by thin layer chromatography (tlc). Aqueous work-up and neutralization of the reaction mixture resulted in almost exclusive formation of thiophenol. Since the above reaction took place very fast, we carried out the reaction at a somewhat lower temperature, however, even at $-15^{o}C$ no nitrile trapping took place and the formation of thiophenol was only observed. This clearly indicated that the reactivity of the trifluoroacetate anion, under the present reaction conditions, was sufficiently high compared to the nitrile, to form the trifluoroacetylmethyl phenyl sulphide which upon aqueous work-up resulted in decomposition to the thiol (Scheme I.32). Such a reaction has a precedent in the literature, albeit in the absence of a nitrile.



SCHEME I.32

It occurred to us that a combination of TFAA-$BF_3.Et_2O$ may reduce the reactivity of the <u>in situ</u> generated trifluoroacetate anion by complexing with BF_3Et_2O and thereby relatively increasing the potential of the nitrile as a nucleophile. Thus, treatment of thioanisole sulphoxide in excess of acetonitrile with a 1.5:3 molar equivalents of TFAA:$BF_2.Et_2O$ at $-10^{o}C$ followed by gradual increase in temperature ($25^{o}C$) and allowing the reaction to continue for a prolonged time did although indicate the


a
CH3
N
H
H
b
S
Aromatic
b
a
TMS
8
7
6
5
4
3
2
0
δ (ppm)

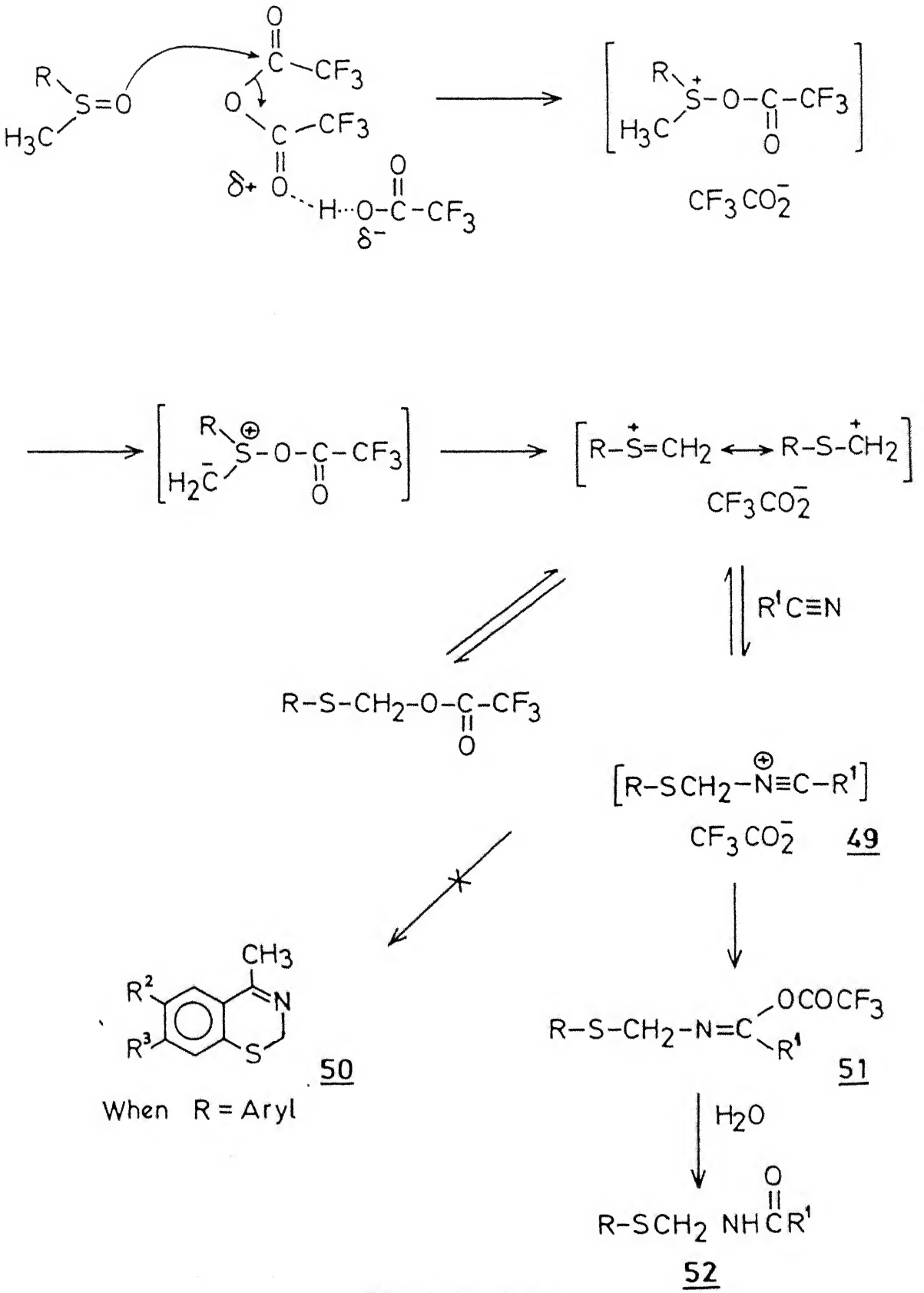
disappearance of the starting sulphoxide, only a small amount (8%) of 4-methyl,2H-benzothiazine (41) (Scheme I.30) was formed along with thiophenol upon work-up. The IR spectrum of 41 showed an absorption at 1600 cm^{-1} ($\nu_{C=N}$) and ^1H NMR indicated absorptions at δ 2.26 (s, 3H, -N=C-CH_3), 4.33 (s, 2H, -S-CH_2-) and 7.1-7.7 (m, 4H, aromatic). The mass spectrum showed a molecular ion peak at 163 (M^+). These spectral characteristics were identical with those reported earlier[31] for the 2H-benzothiazine derivative 41. It is therefore apparent that the intermediate 48 was formed, though in small yield, and then underwent cyclization to give the 2H-benzothiazine derivative 41. No trace of the amide 42, however, was obtained.

The low yield of the Ritter reaction product from a Pummerer intermediate, generated under the above conditions, viz. by the use of $BF_3.Et_2O$ for complexation with the trifluoroacetate anion, led us to look for an alternate electrophilic system. As mentioned in the background part of Pummerer reaction, a combination of TFAA and trifluoroacetic acid (TFA) has been used as an excellent electrophilic system for successful realization of Pummerer rearrangement by not allowing the attack of trifluoroacetate anion on the Pummerer intermediate (cf. Scheme I.26). This system, i.e., TFAA/TFA thus appeared to be ideal for our study. Initially when thioanisole sulphoxide (43a)(Scheme I.31) in excess nitrile was treated with a mixture of TFAA and 4-5 fold excess of TFA (cf. Experimental) for a prolonged time the expected amide, N-(phenylthiomethyl)-

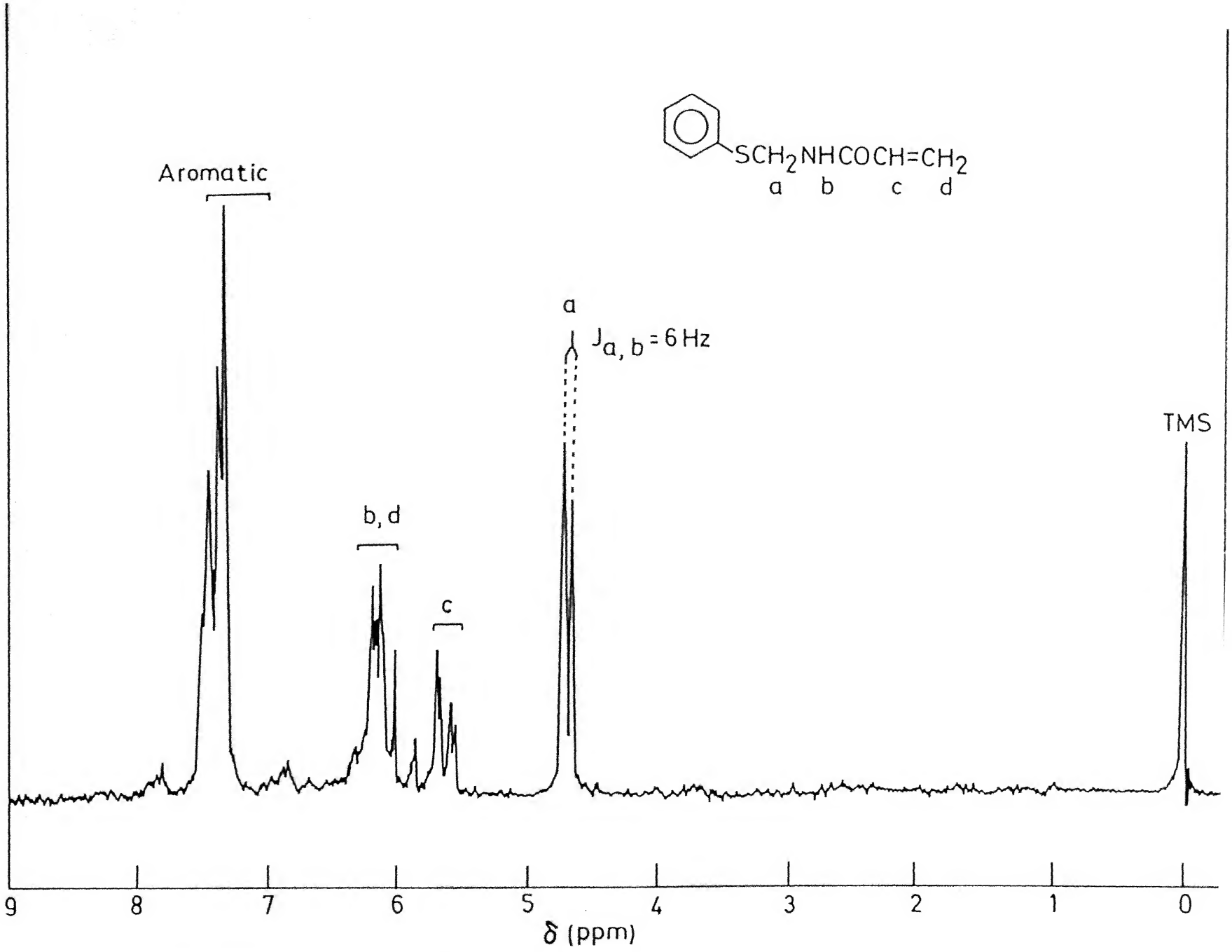
acetamide (45a) was obtained in 45% yield, m.p. 45°C (lit.[32] m.p. 45-46°C). The IR spectrum of this amide showed a strong absorption at 1675 cm^{-1} (ν_{C-NH}^{O}) and ^1H NMR indicated absorptions at δ 1.90 (s, 3H, -NH-$\overset{O}{\overset{\|}{C}}$-$CH_3$), 4.63 (d, 2H, J = 6 Hz, -S-CH_2-), 7.16-7.47 (m, 5H, aromatic). Mass spectrum showed M^+ peak at 181. These data confirm the structure of the amide 45a. Although no cyclized product i.e., 2H-benzothiazine derivative (41) was formed, interestingly a disulphide 46a was obtained, m.p. 40°C (lit.[33] m.p. 40-41°C). This showed ^1H NMR absorptions at δ 4.35 (s, 2H, -S-CH_2-) and 7.1-7.77 (m, 10 H, aromatic) and its mass spectrum showed a M^+ peak at 232. Thioanisole sulphoxide was also reacted with acrylonitrile and benzonitrile under similar conditions and the corresponding amides 45d and 45f were obtained in 57% and 46% yields, respectively along with 38% of the disulphide 46a in each case.

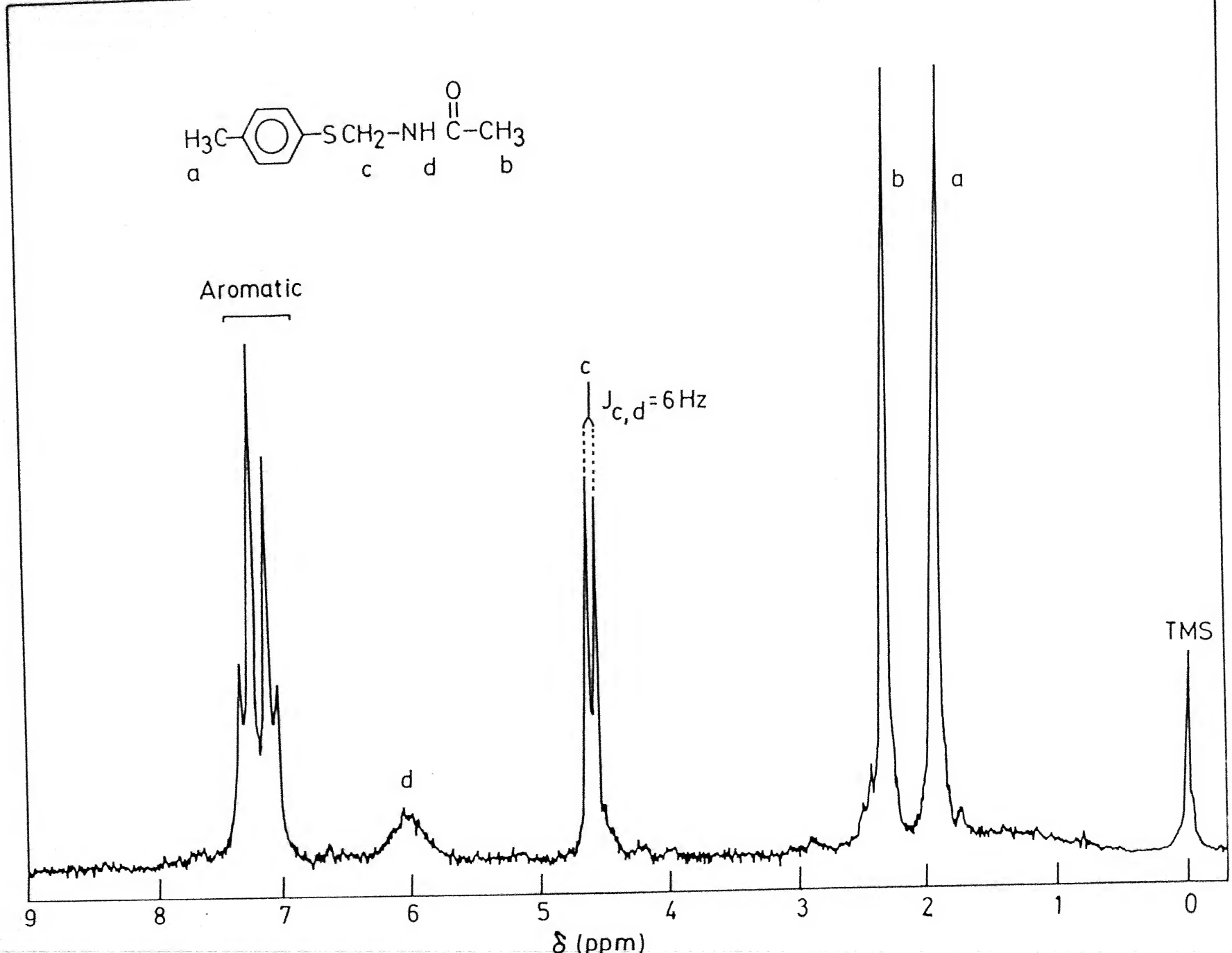
Other sulphoxides viz., 4-methylthioanisole sulphoxide (43b) and dimethylsulphoxide (47) also reacted with acetonitrile, acrylonitrile and benzonitrile under similar conditions leading to the formation of the corresponding amides 45b, 45e, 45g and 45h, 48i, 48j, in an analogous manner as above. The results are summarized in Scheme I.31. The structures assigned to these products were again based on their spectral and analytical data (cf. Experimental).

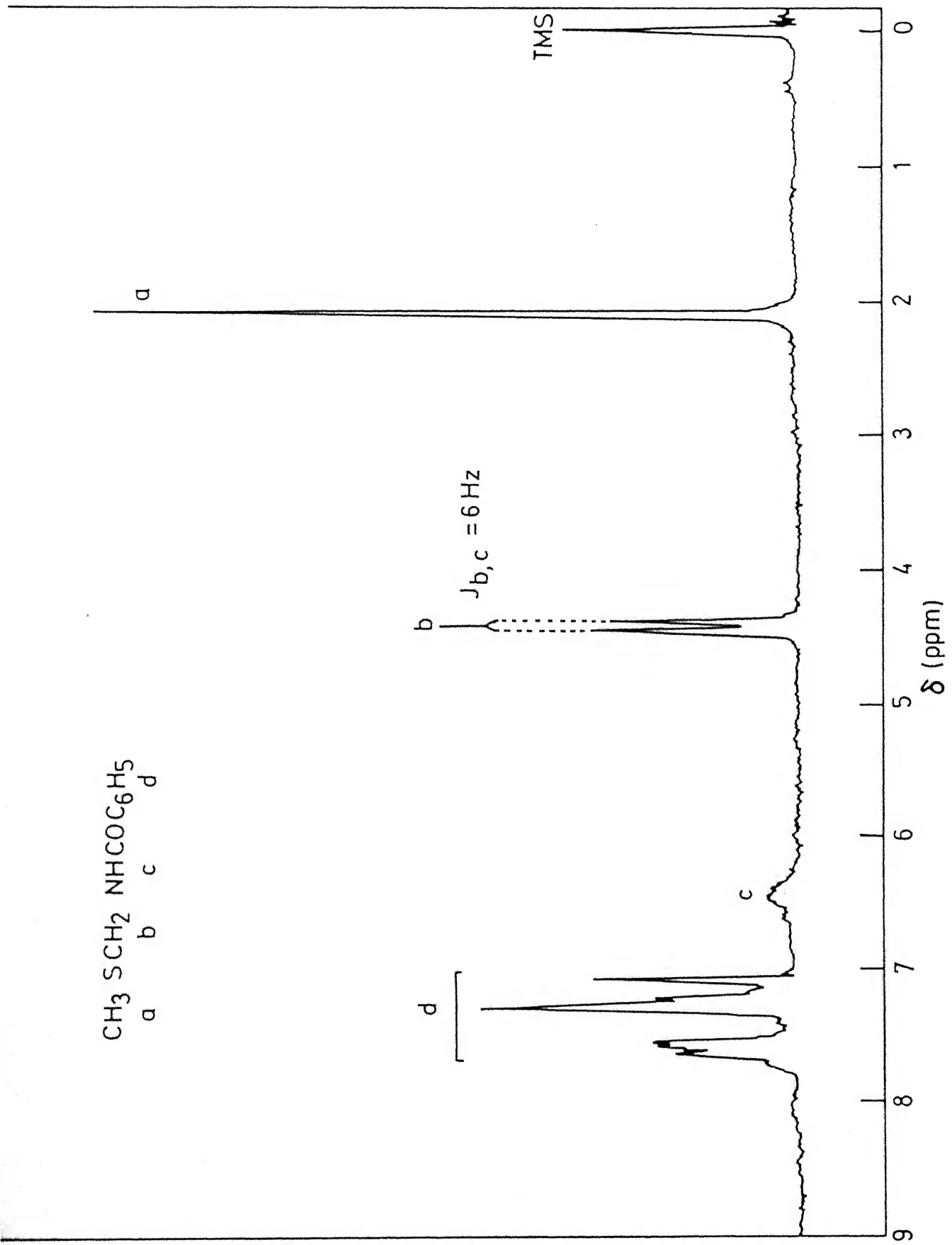
The formation of amides under the above mentioned conditions, thus, seems to be a general case and a probable mechanism is delineated in Scheme I.33.

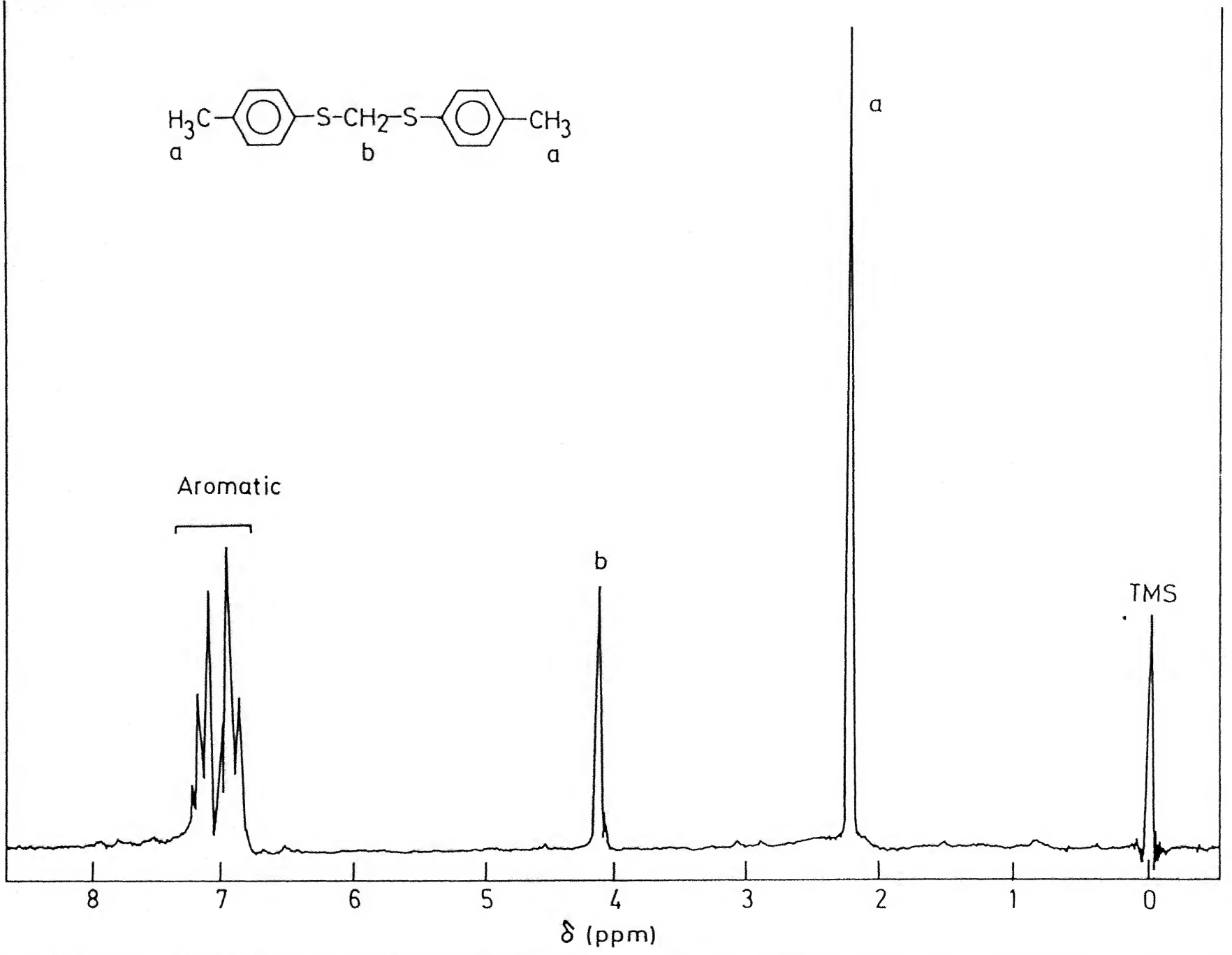


SCHEME 1·33


SCH2NHCOCH=CH2
a b c d
Aromatic
a
Ja, b = 6 Hz
b, d
c
TMS
9
8
7
6
5
4
3
2
1
0
δ (ppm)

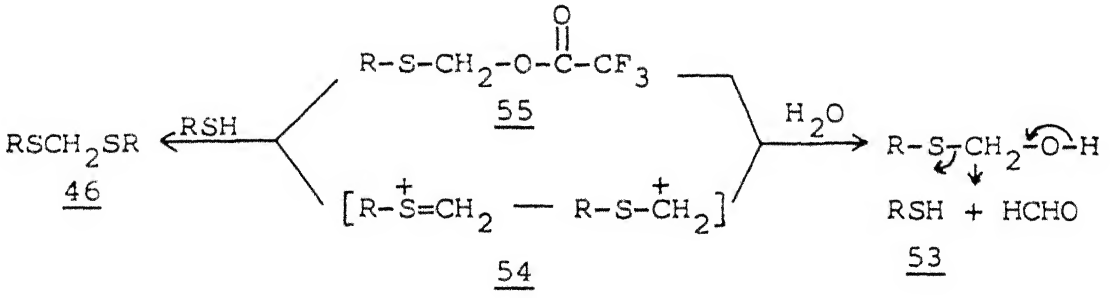

H3C
S CH2–NH C–CH3
O
a
c
d
b
Aromatic
c
Jc, d = 6 Hz
b
a
TMS
d
9
8
7
6
5
4
3
2
1
0
δ (ppm)


CH3 SCH2 NHCOC6H5
a b c d
TMS
a
b
Jb,c = 6 Hz
c
d
0
1
2
3
4
5
6
7
8
9
δ (ppm)

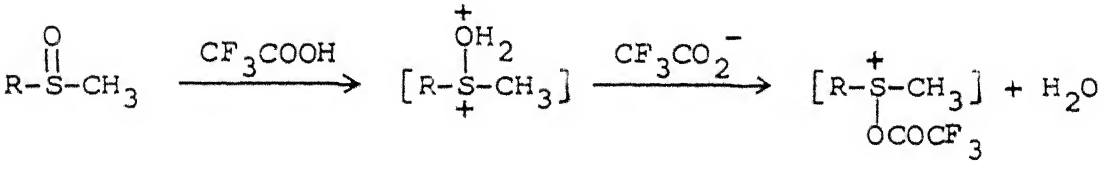

H3C
a
S-CH2-S
b
CH3
a
a
Aromatic
b
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

The fact that no trace of a cyclized product 50 was obtained in any case indicated that the nitrilium ion intermediate 49 was preferentially attacked by the CF_3COO^- than by the aromatic ring to give 51, which hydrolysed on basic work-up to give the amide 52. It then occurred to us that an increase in electron density on aromatic ring of the sulphoxide might result in the formation of a cyclized product. With this view in mind when m-methoxy thioanisole sulphoxide (43c) was reacted with acetonitrile under similar conditions as before, again only the amide 45c was formed along with the disulphide 46c (cf. Experimental for spectral data). The failure to obtain any cyclized product even in this case, though surprising, strongly indicated that the formation of imine 51 was fast and irreversible. It could thus be concluded, that cyclization could occur only in cases where the counter-ion (CF_3COO^-, in the present case), is not at all nucleophilic.

The formation of disulphides 46 (Scheme I.34) is interesting, which is possible only if free thiol 53 is somehow produced in the reaction to react with 54. In view of the fact that the intermediate 54 and the trifluoroacetyl derivative 55 both react with water to produce formaldehyde and free thiol, it is likely that some water is produced during the reaction. Literature survey indicates that sulphoxides do ionize in strongly acidic medium[34] to produce sulphonium salts of the type 57 through the intermediacy of 56 by eliminating water (Scheme I.35). It is, therefore, not surprising that under



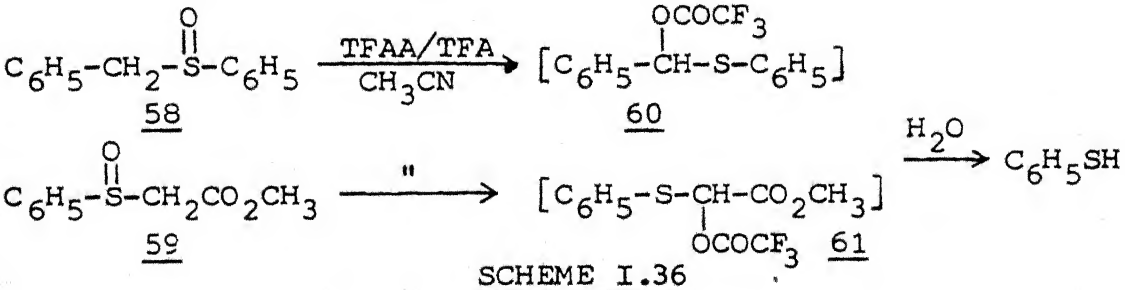
SCHEME I.34



SCHEME I.35

the present reaction conditions some ionization of sulphoxides of this type is possible which eventually results in the formation of disulphide 46.

Two more sulphoxides viz., benzyl phenyl sulphoxide 58 and α-(phenylsulphinyl)methyl acetate (59) (which have phenyl ring and an ester group, respectively on the carbon α to the sulphoxide) were used in our study. Initial reaction with acetonitrile on both the cases led to the formation of thiol, indicating the formation of α-trifluoroacetates (60 and 61) which decompose to thiol on work-up (Scheme I.36). Literature



SCHEME I.36

survey does indicate that highly stabilized and highly destabilized carbocations do not undergo Ritter reaction. It was therefore not surprising to witness failures of Ritter reaction on Pummerer intermediates derived from these compounds.

I.A.3 Experimental

All reactions were performed in oven dry apparatus under dry nitrogen atmosphere. Reaction mixtureswere stirred magnetically, unless otherwise specififed.

All the melting points are uncorrected and were taken on Fischer-Johns melting point apparatus.

Infrared (IR) spectra were recorded on Perkin-Elmer model 377, 580 and 1320 spectrometers, and are reported in wave numbers.

Proton magnetic resonance (PMR) spectra were recorded on Bruker WP-80 (80 MHz), EM-390 (90 MHz), Hitachi FTR-600 (60 MHz) and Varian HA-100 (100 MHz) instruments. Chemical shifts are reported in parts per million (ppm) downfield from internal reference tetramethylsilane (δ). Multiplicity is indicated using the following abbreviations: s (singlet), br (broad), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (J) are reported wherever necessary and are expressed in Hz.

Mass spectra were recorded on Jeol JMS-300D Mass Spectrometer at 70 eV. The elemental analyses were carried out in Coleman automatic carbon, hydrogen and nitrogen analysers.

Starting Materials

Commercial grade solvents were distilled prior to use. Acetonitrile was dried by first storing over anhyd. $CaCl_2$ for

at least 24 hrs. It was then distilled twice over P_2O_5. Acrylonitrile and benzonitrile were both dried by refluxing over CaH_2 and then distilling. Methylene chloride used for the reactions was distilled over P_2O_5. Dimethyl sulphoxide was dried by first freezing at 5°C, removing the unfrozen liquid, and distilling twice over CaH_2, and was stored on molecular sieves (4 Å). Trifluoroacetic acid and trifluoroacetic anhydride were both purchased from Fluka AG, and were distilled at their boiling points prior to use. Boron trifluoride etherate was purchased from Fluka and was distilled under reduced pressure over CaH_2 prior to use.

Thioanisole sulphoxide and p-methylthioanisole sulphoxide were prepared by the literature procedure,[35] by oxidizing the corresponding sulphides with Br_2-$KHCO_3$ in CH_2Cl_2-H_2O biphase system. m-Methoxythioanisole sulphoxide was prepared by oxidising m-methoxythioanisole with sodium metaperiodate[36] in methanol.

Reaction of Thioanisole Sulphoxide with Acetonitrile: Formation of N-[(phenylthio)methyl]acetamide (45a) and (46a)

To a stirred solution of thioanisole sulphoxide (350 mg, 2.5 mmol) in 5 ml dry acetonitrile, under nitrogen atmosphere, at 0°C was added a mixture of trifluoroacetic anhydride (0.46 ml, 3.25 mmol) and trifluoroacetic acid (1 ml, 13 mmol) in 1 ml of dry dichloromethane, dropwise over a period of 30 min. After the addition was completed the reaction mixture was allowed to stir for 8 hrs at 0°C, then brought to room temperature and continued to stir at room temperature for additional 48 hrs. The

reaction mixture was then cooled to 0°C, and a cold aqueous solution of 2 N (8%) sodium hydroxide was added slowly till the solution was just basic to litmus (about 8 ml was required). The reaction mixture was diluted with another 5 ml of water, and extracted thrice with 15 ml portions of dichloromethane. The combined dichloromethane layers were washed with water (10 ml) and then with brine (10 ml), and then dried over anhydrous sodium sulphate. The solvent was evaporated on a rotary evaporator and the last traces of solvent removed under vacuum. The crude product so obtained was separated by thick layer chromatography (silica gel) using benzene:acetone (85:15) as eluent to obtain two products. The more polar compound, N-[(phenylthio)methyl]acetamide (45a) was obtained as a crystalline solid (yield: 203 mg, 45%), m.p. 45°C (lit.[32] 45-46°C).

IR ($CHCl_3$) ν_{max} (cm^{-1}): 1675 ($\nu_{C=O}$), 3300 (br ν_{N-H}), 3440 (m ν_{N-H}).

PMR ($CDCl_3$) δ(ppm): 1.90 (s, 3H, $COCH_3$), 4.63 (d, 2H, J = 6 Hz, $-S-CH_2$), 7.16-7.47 (m, 5H, aryl).

Mass spectrum, m/e (rel. ab.): 181 (11, M^+), 110 (39, $M^+-CH_2=N-COCH_3$), 109 (25, $M^+-CH_2NHCOCH_3$), 72 (56), 43 (100).

Analysis for $C_9H_{11}NOS$: Calcd. C, 59.67; H, 6.08; N. 7.73.
Found: C, 59.92; H, 5.91; N, 7.39%.

The less polar compound (46a), was obtained as thick oil, which was recrystallized from ethanol, m.p. 40°C (lit.[33] m.p. 40-41°C), yield: 104 mg, 36%.

PMR (CCl_4), δ(ppm): 4.35 (s, 3H, $-SC\underline{H}_3$), 7.1 - 7.7 (m, 10H, aryl).

Mass spectrum, m/e (rel. ab.): 232 (45, M^+), 123 (100, $M^+ - SC_6H_5$), 109 (20), 77 (15).

Reaction of p-Methylthioanisole Sulphoxide with Acetonitrile: Formation of N-[4-methylphenylthio)methyl]acetamide (45a) and (46b)

The reaction was performed in the same manner as with thioanisole sulphoxide. 385 mg (2.5 mmol) of p-methylthioanisole sulphoxide 0.46 ml (3.25 mmol) of TFAA and 1 ml (13 mmol) of TFA were reacted to yield after thick layer chromatographic separation the amide (45b) as crystalline solid, m.p. 97°C (yield: 195 mg, 40%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1675 ($\nu_{C=O}$), 3300 (br, ν_{C-N}), 3440 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.90 (s, 3H, $CO-C\underline{H}_3$), 2.30 (s, 3H, $ArC\underline{H}_3$), 4.57 (d, 2H, J = 6 Hz, $-S-C\underline{H}_2-$), 6.03 (br, s, H, $-N\underline{H}-$), 6.87 - 7.5 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 195 (69, M^+), 124 (100, $M^+ - CH_2{=}N{-}COCH_3$), 91 (17), 72 (16).

Anal. for $C_{10}H_{13}NOS$: Calcd.: C, 61.54; H, 6.67; N, 7.18.
Found : C, 61.08; H, 6.67; N, 7.33%.

The other product 46b, was obtained as a thick oil which was recrystallized from ethanol, m.p. 31.5°C (lit.[33] m.p. 32°C) (yield: 116 mg, 36%).

PMR (CCl_4), δ(ppm): 2.27 (s, 6H, Ar-CH_3), 4.17 (s, 2H, S-CH_2), 6.83-7.4 (m, 8H, aryl).

Mass spectrum, m/e (rel. ab.): 260 (19, M^+), 137 (25, M^+-$SC_6H_4CH_3$), 123 (18), 91 (100).

Reaction of Thioanisole Sulphoxide with Acrylonitrile: Formation of N-[(phenylthio)methyl]propenamide (45d) and (46a)

This reaction was carried out exactly as on the same scale and for the same reaction time, but using acrylonitrile instead of acetonitrile. For thick layer chromatographic elution benzene: acetone, 9:1 was used.

The amide (45d) was obtained as a thick oil (yield: 273 mg, 57%).

IR (thin film), ν_{max} (cm^{-1}): 1635 ($\nu_{C=C}$), 1675 ($\nu_{C=O}$), 3300 (ν_{N-H}).

PMR ($CDCl_3$), δ(ppm): 4.81 (d, 2H, J = 6.25 Hz, S-CH_2), 5.53-6.68 (m, 2H, vinyl), 7.28-7.96 (m, 5H, aryl).

Mass spectrum, m/e (rel. ab.): 193 (43, H^+), 110 (22, M^+-CH_2:NCOCH:CH_2), 109 (13, M^+-$CH_2NHCOCH:CH_2$), 84 (82), 55 (100).

Anal. for $C_{10}H_{11}NOS$: Calcd.: C, 62.18; H, 5.70; N, 7.25.
Found : C, 62.51; H, 5.78; N, 7.41%.

The disulphide 46a obtained was 100 mg (38% yield) with m.p. 40°C.

Reaction of p-Methylthioanisole Sulphoxide with Acrylonitrile: Formation of N-[(4-methylphenylthio)methyl]propenamide (45e) and (46b)

The reaction was carried out in the same manner as described above for the preparation of 45d using 385 mg (2.5 mmol) of para-methyl thioanisole sulphoxide, for the same reaction time (48 hr). The amide 45e was obtained as a crystalline solid, m.p. 77°C, yield: 207 mg, 43%.

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1630 ($\nu_{C=C}$), 1675 ($\nu_{C=O}$), 3295 (br, ν_{N-H}), 3430 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 2.32 (2.32 (s, 3H, Ar-CH_3), 4.68 (d, 2H, J = 6 Hz, S-CH_2), 5.50-6.40 (m, 3H, vinyl), 6.93-7.43 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 207 (47, M^+), 124 (63, M^+-CH_2=NCOCH:CH_2), 123 (18, M^+-CH_2NHCOCH:CH_2), 91 (18), 55 (100).

Anal. for $C_{11}H_{13}NOS$: Calcd.: C, 63.77; H, 6.28; N, 6.76.
Found : C, 64.08; H, 6.48; N, 6.90%.

The disulphide 46b obtained was 156 mg (48% yield) with m.p. 32°C.

Reaction of Thioanisole Sulphoxide with Benzonitrile: Formation of N-[(phenylthio)methyl]benzamide (45f) and (46a)

The reaction was carried out as described in earlier experiments (cf. preparation of 45a and 45b), using thioanisole sulphoxide (2.5 mmol) and benzonitrile (5 ml) for 72 hr. After the reaction was over, the excess benzonitrile and trifluoro-

acetic acid were removed under reduced pressure (about 5 mm). The residue was then treated with ice cold aq. NaOH (5% solution) and worked up as described before. Thick layer chromatographic elution was done with benzene:acetone (9:1) to give the amide 45f as a crystalline solid, m.p. 66°C (lit.[37] m.p. 67°C), 280 mg, 46%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1660 ($\nu_{C=O}$), 3280 (br, ν_{N-H}), 3430 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 4.93 (d, 2H, J = 6.25, -S-$C\underline{H}_2$), 6.84 (br, 1H, -$\underline{N}$H-), 7.19-8.16 (m, 10H, aryl).

Mass spectrum, m/e (rel. ab.): 243 (13, M^+), 134 (36, M^+-SC_6H_5), 110 (9, M^+-CH_2:$NCOC_6H_5$), 109 (22, M^+-$CH_2NHCOC_6H_5$), 105 (100).

Anal. for $C_{14}H_{13}NOS$: Calcd.: C, 69.14; H, 5.35; N, 5.76.
Found : C, 68.75; H, 5.27; N, 5.51%.

The disulphide 46a was obtained in 38% yield (110 mg), m.p. 40°C.

Reaction of p-Methylthioanisole Sulphoxide with Benzonitrile: Formation of N-[(4-methylphenylthio)methyl]benzamide (45g) and (46b)

Following the previous procedure reaction of 2.5 mmol of p-methylthioanisole sulphoxide for 48 hr, gave the amide (45g), m.p. 106-107°C (yield: 269 mg, 57%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1660 ($\nu_{C=O}$), 3280 (br, ν_{N-H}), 3440 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 2.30 (s, 3H, Ar-CH_3), 4.85 (d, 2H, J = 6 Hz, S-CH_2), 6.65 (br, 1H, -NH-), 7.0-7.9 (m, 9H, aromatic).

Mass spectrum, m/e (rel. ab.): 257 (54, M^+), 166 (28, M^+-$C_2H_4CH_3$), 134 (25, M^+-$SC_6H_4CH_3$), 105 (100).

Anal. for $C_{15}H_{15}NOS$: Calcd.: C, 70.04; H, 5.84; N, 5.45.
Found : C, 69.89; H, 5.57; N, 5.29%.

The disulphide 46b was obtained in 35% yield (114 mg), m.p. 32°C.

Reaction of Dimethyl Sulphoxide with Acetonitrile: Formation of N-[(methylthio)methyl]acetamide (48h)

The reaction was carried out in the same way as done with thioanisole sulphoxide with 0.250 g (3.21 mmol) dimethyl sulphoxide in 5 ml acetonitrile, TFAA (0.68 ml, 4.82 mmol) and TFA (1.3 ml, 17 mmol). After 24 hr of reaction, the excess acetonitrile and TFA were removed under vacuum and the residue treated with 4 ml of ice cold aq. NaOH solution, saturated the solution with solid sodium chloride, and extracted with ethyl acetate. Evaporation of the solvent gave a crude product, which was washed twice with pentane (5 ml each). The pentane layer was discarded and the crude product was purified by thick layer chromatography (silica gel) with benzene:acetone, 80:20 as eluent. The amide 48h was obtained as a thick oil (yield: 133 mg, 35%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1665 ($\nu_{C=O}$), 3320 (br, ν_{N-H}), 3425 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 2.03 (s, 3H, $COC\underline{H}_3$), 2.17 (s, 3H, $SC\underline{H}_3$), 4.37 (d, 2H, J = 6 Hz, $SC\underline{H}_2$), 6.17 (br, 1H, -N<u>H</u>-).

Mass spectrum, m/e (rel. ab.): 119 (45, M^+), 72 (100, M^+--SCH_3), 61 (8, M^+-$NHCOCH_3$), 47 (9), 43 (92).

Anal. for C_4H_9NOS: Calcd.: C, 40.34; H, 7.56; N, 11.76.
Found : C, 40.74, H, 7.18; N, 11.37%.

Reaction of Dimethylsulphoxide with Acrylonitrile: Formation of N-[(methylthio)methyl]propenamide (48i)

Repeating the earlier reported reaction of dimethyl sulphoxide with acrylonitrile in place of acetonitrile for 24 hr, gave 0.125 g (30%) of the amide 48i.

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1625 ($\nu_{C=C}$), 1670 ($\nu_{C=O}$), 3290 (br, ν_{N-H}), 3430 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 2.17 (s, 3H, $SC\underline{H}_3$), 4.45 (d, 2H, J = 6 Hz, $SC\underline{H}_2$), 5.58-6.46 (m, 3H, vinyl).

Mass spectrum, m/e (rel. ab.): 131 (15, M^+), 84 (68, M^+-SCH_3), 43 (100).

Anal. for C_5H_9NOS: Calcd.: C, 45.80; H, 6.87; N, 10.69.
Found : C, 45.39; H, 6.79; N, 10.48%.

Reaction of Dimethyl Sulphoxide with Benzonitrile: Formation of N-[(methylthio)methyl]benzoamide (48j)

Using the same reaction conditions as described in the earlier methods (cf. reaction of dimethyl sulphoxide with aceto-

nitrile) but by using benzonitrile for 24 hr, gave after purification (by thick layer chromatography), 48j as a crystalline solid, m.p. 104°C (lit.[38] 105°C) (yield: 307 mg, 53%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1660 ($\nu_{C=O}$), 3300 (br, ν_{N-H}), 3440 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 2.13 (s, 3H, $SC\underline{H}_3$), 4.50 (d, 2H, J = 6 Hz), 6.57 (br, 1H, N$\underline{H}$), 7.2 - 7.93 (m, 5H, aromatic).

Mass spectrum, m/e (rel. ab.): 181 (35, M^+), 134 (35, $M^+ - SCH_3$), 105 (100), 77 (46).

Anal. for $C_9J_{11}NOS$: Calcd.: C, 59.67; H, 6.08; N, 7.73.
Found : C, 59.24; H, 6.11; N, 7.43%.

Reaction of m-Methoxythioanisole Sulphoxide with Acetonitrile: Formation of N-[(3-methoxyphenylthio)methyl]acetamide (45c) and (46c)

The reaction was carried out in the same manner as done with thioanisole sulphoxide, by using m-methoxythioanisole sulphoxide (0.150 g, 0.88 mmol), TFAA (0.19 ml, 1.32 mmol) and TFA (0.35 ml), in acetonitrile for 48 hr. Separation of the crude product by thick layer chromatography (benzene:acetone, 80:20 for elution) gave the amide 45c as a gum, yield: 0.075 g, 40%.

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1675 ($\nu_{C=O}$), 3300 (br, ν_{N-H}), 3440 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.90 (s, 3H, $COC\underline{H}_3$), 3.74 (s, 3H, $-OC\underline{H}_3$), 4.64 (d, 2H, J = 6 Hz, $-S-C\underline{H}_2$), 6.6 - 7.2 (m, 4H aryl).

Mass spectrum, m/e (rel. ab.): 211 (17, M^+), 140 (100, $M^+-CH_2:NCOCH_3$), 72 (16, $M^+-SC_6H_4OCH_3$).

Anal. for $C_{10}H_{13}NO_2S$: Calcd.: C, 56.87; H, 6.16; N, 7.11.
Found : C, 55.98; H, 6.02; N, 6.99%.

The second product, the disulphide 46c was also obtained as a gum (yield: 0.052 g, 40%).

PMR ($CDCl_3$), δ (ppm): 3.75 (s, 6H, $-OCH_3$), 4.1 (s, 2H, SCH_2), 6.7 - 7.2 (m, 8H, aryl).

Mass spectrum, m/e (rel. ab.): 292 (100, M^+), 153 (25, $M^+-SC_6H_4OCH_3$).

Anal. for $C_{15}H_{16}O_2S$: Calcd.: C, 61.64; H, 5.48.
Found : C, 61.36; H, 5.37%.

Reaction of Thioanisole Sulphoxide with Acetonitrile, Using TFAA-$BF_3.Et_2O$: Formation of 4-Methyl-2H-1,3-benzothiazine (41)

To a stirred solution of thioanisole sulphoxide (0.200 g, 1.43 mmol) in 2 ml acetonitrile at 0°C, was added a mixture of TFAA (0.3 ml, 2.1 mmol) and $BF_3.Et_2O$ (0.53 ml, 4.3 mmol) in 1.0 ml acetonitrile, dropwise, in about 30 min. time. The reaction was stirred at -10°C for 8 hr and then at room temperature for 24 hr. A cooled 2N NaOH solution was added to the reaction mixture at 0°C till basic to litmus and extracted with ethyl acetate (3 x 10 ml). Extraction of the aq. layer with ether after acidification with 6N HCl and evaporation of the solvent gave thiophenol (yield: 0.134 g, 85%), b.p. 169°C (lit.[39] b.p. 169.7°C).

Evaporation of the ethyl acetate layer under reduced pressure gave crude product, which on purification by thick layer chromatography (silica gel) with eluents benzene:acetone:: 80:20, gave the benzothiazine 41 as an oil (yield: 0.020 g, 8.6%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1600 ($\nu_{C=N}$).

PMR ($CDCl_3$), δ (ppm): 226 (s, 3H, -N=C-C$\underline{H}_3$), 4.33 (s, 2H, SC$\underline{H}_2$) and 7.10-7.7 (m, 4H, aromatic).

Mass spectrum, m/e (rel. ab.): 163 (90, M^+), 162 (100), 148 (80), 134 (90), 123 (72), 121 (70), 90 (85).

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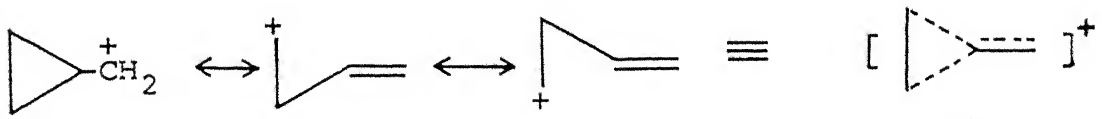
PART-B: RITTER REACTION ON CYCLOPROPYL CARBINOLS AND CYCLOPROPYL KETONES

I.B.1 Background

Cyclopropanes, because of their structural characteristics, are highly strained and fragile systems. When a cation is generated α- to the cyclopropyl ring, the system 62 relieves its strain by conjugation of the bent (sp^5) orbitals of the cyclopropyl ring, with the vacant p-orbital of the carbenium ion,[1,2] resulting in the opening of the three membered ring and formation of a homoallyl cation 63 .[3] This cyclopropylmethyl-homoallyl rearrangement (Scheme I.37) plays a

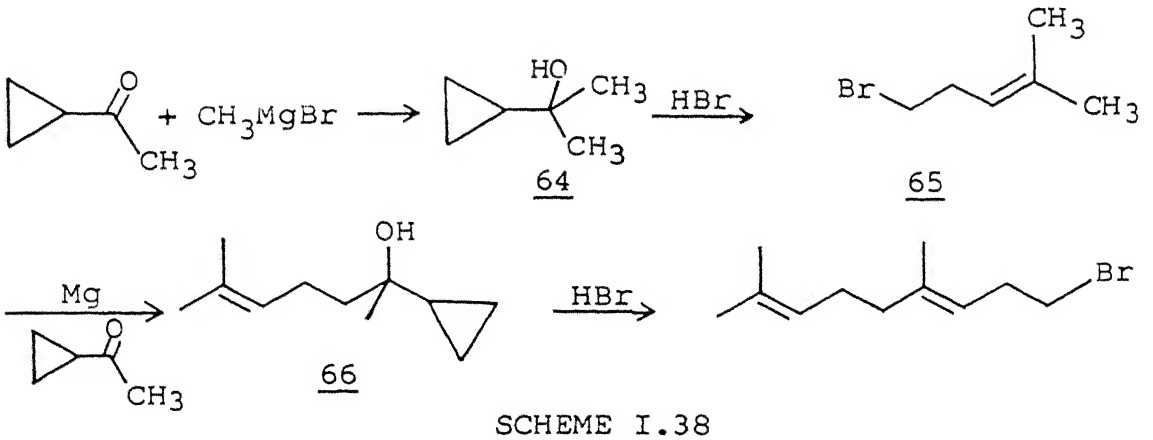


62 63

SCHEME I.37

major role in synthetic utilization of the cyclopropyl ring function.[4] It has found wide application in the preparation of isoprenoids.

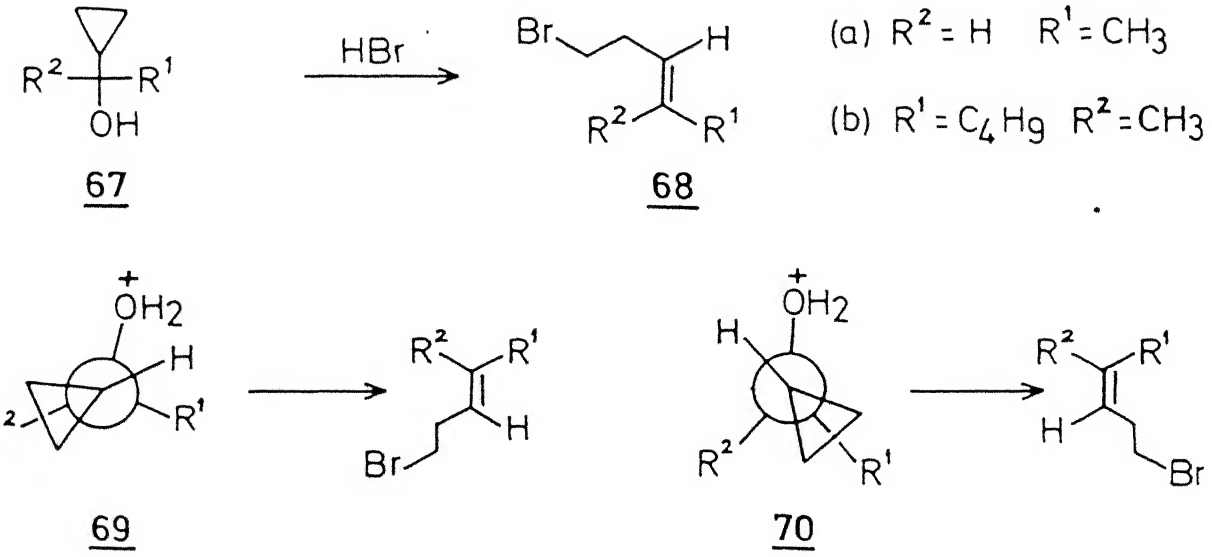
Julia et al.[5] were the first to exploit the synthetic utility of cyclopropylcarbinyl-homoallyl rearrangement. They treated the carbinol 64 with HBr to get the homoallyl bromide 63 , which was utilized to generate the carbinol 66 . Repetition of the sequence of reaction on 66 led to the synthesis of long chain isoprenoids (Scheme I.38).



SCHEME I.38

When the secondary cyclopropyl carbinol 67a was treated with HBr, the trans-homoallyl bromide 68 was formed with 90-95% stereoselectivity (Scheme I.39). However, with the tertiary carbinol 67b , the reaction was not stereoselective, giving both E and Z isomers in the ratio 3:1. This can be visualized from the Newman projection of the transition states 69 and 70 . If R^2 = H (67a) then clearly the transition state 69 which leads to the trans olefin is favoured over the transition state 70 . But if R^1 and R^2 are substituents with somewhat similar steric requirement (67b) then there will be no great preference for one transition state over the other.

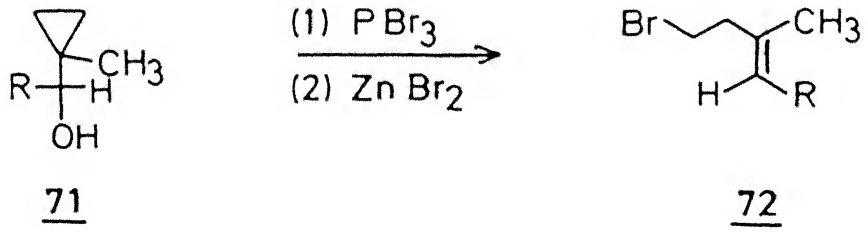
With methylcyclopropyl carbinols of the type 71, treatment with phosphorus tribromide followed by anhydrous zinc bromide in ether affords trans-substituted ethylenes 72 in good yield and with a high degree of stereoselectivity.[6] Thus, the alcohol 73 was converted to the trans diene 74 without any isomerization of the terminal double bond (Scheme I.40). The reason for the high stereoselectivity can be predicted from the Newman projection formulae 75 and 76 . Because of less steric



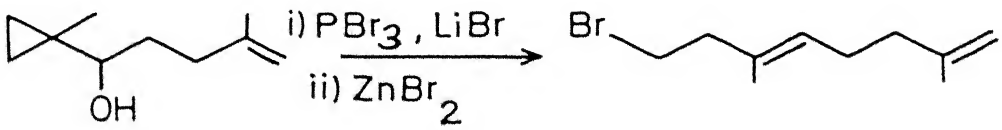
67 68

69 70

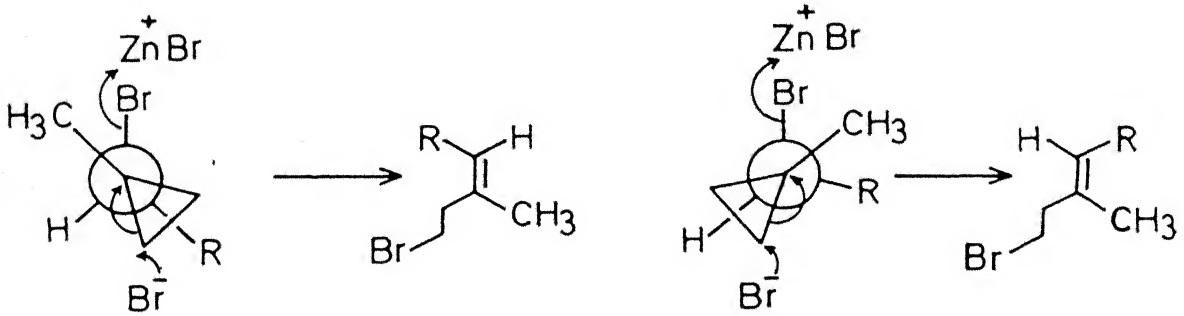
SCHEME I·39



71 72



73 74

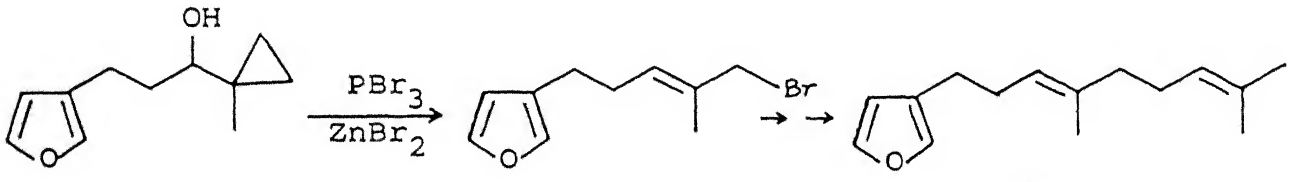


75 76

SCHEME I·40

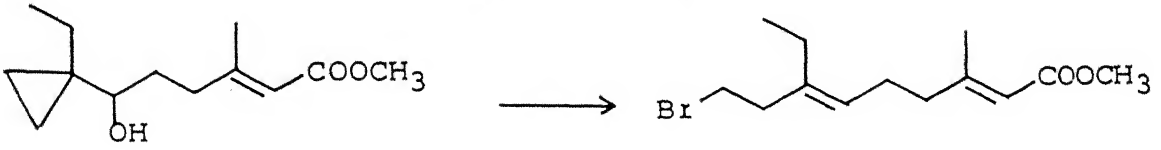
interactions, between the cyclopropane ring and substituent R, conformation 76 is preferred, which leads to the E-olefin.

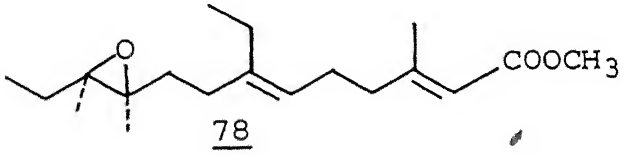
The highly stereoselective ring opening of methylcyclopropyl carbinol system to give homoallylic system with trans-substituted internal double bond, was utilized as the key step in the synthesis of a natural product dendrolasin (77) by Parker and Johnson[7] (Scheme I.41) and also for the synthesis of the cecropia juvenile hormone 78 by Johnson et al.[8] (Scheme I.42).



77

SCHEME I.41

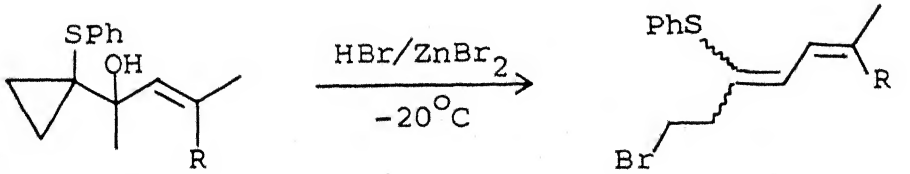




78

SCHEME I.42

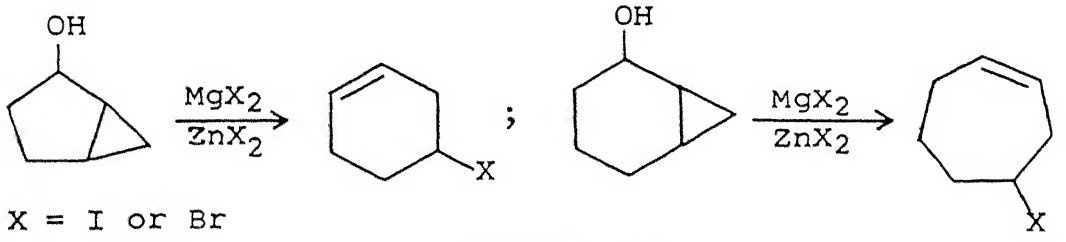
Miller et al.[9] have reported the acid catalysed rearrangement of (phenylthiocyclopropyl)vinyl methanols 79 to functionalised conjugate dienes 80 , which are versatile intermediates in organic synthesis (Eqn. I.5):



..(I.5)

79 80

Magnesium and Berylium halides in refluxing ether have been reported to transform cyclopropyl carbinols to homoallylic halides under mild conditions and in high yields.[10] With bicyclic cyclopropane systems use of magnesium halide/zinc halide combination enhanced rate and increased the regioselectivity of the ring opening (Scheme I.43).[11]



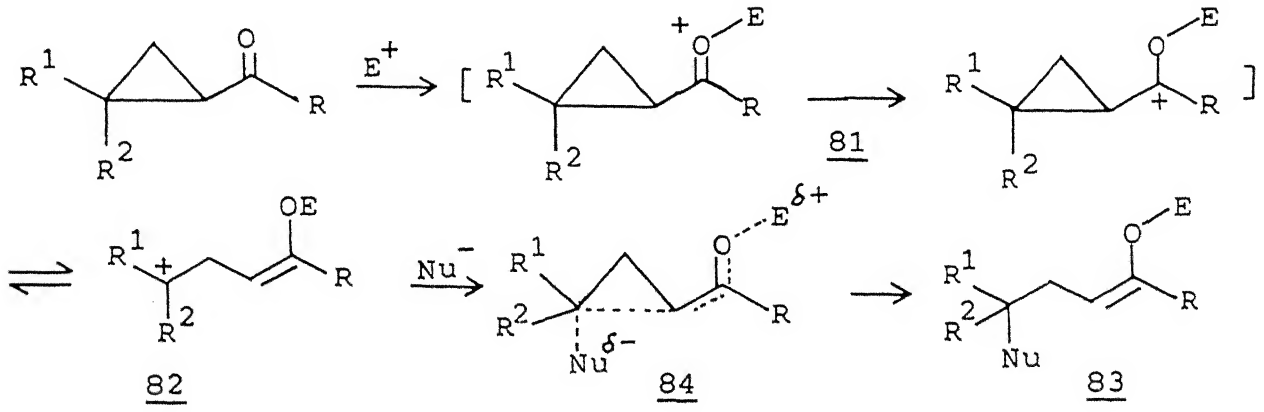
X = I or Br

SCHEME I.43

Recently, phosphorus iodides P_2I_4 and PI_3,[12] and also Ph_3P/I_2[13] have been reported to cleave cyclopropyl carbinols to homoallyl iodides.

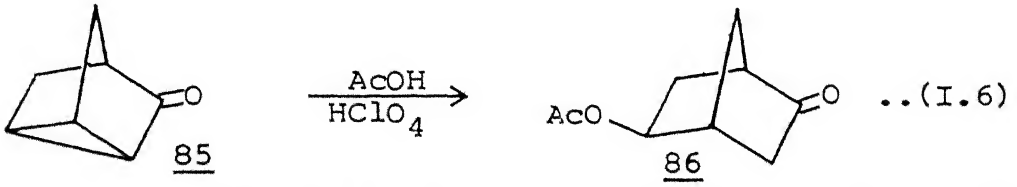
In the case of cyclopropyl carbonyl derivatives, it is possible to open the cyclopropyl ring in diactivated cyclopropanes directly by the attack of nucleophiles,[14] but in the case of monoactivated cyclopropane (cyclopropyl ketones, esters etc.), prior activation by an electrophile is essential for the attack of a nucleophile. Thus, cyclopropyl ketones on treatment with an acid (protic or Lewis), or any other strongly electrophilic reagent, the carbonyl group gets activated to generate a cyclopropylcarbinyl cationic species 81 which by conjugation with the sp^5 bond of cyclopropane ring leads to the homoallylic type cation 82[4] (as in the case of cyclopropyl carbinols). This incipient carbenium ion can be irreversibly trapped by a nucleo-

phile present in the reaction medium. It is proposed that the whole process may take place in a concerted way as shown by the transition state 84[15] (Scheme I.44).



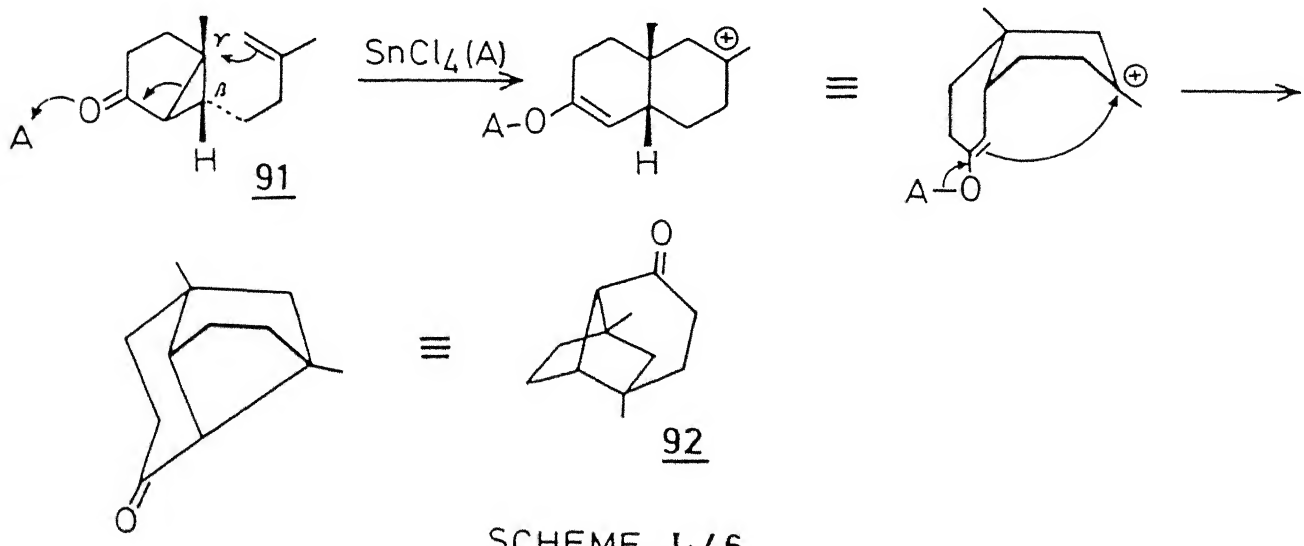
SCHEME I.44

There are several examples of nucleophilic attack on electrophilically activated cyclopropyl ketones in the literature. Thus, nortricyclone (85) with acetic acid-$HClO_4$ mixture gave 5-acetoxy ketone (86)[16] (Eqn. I.6):

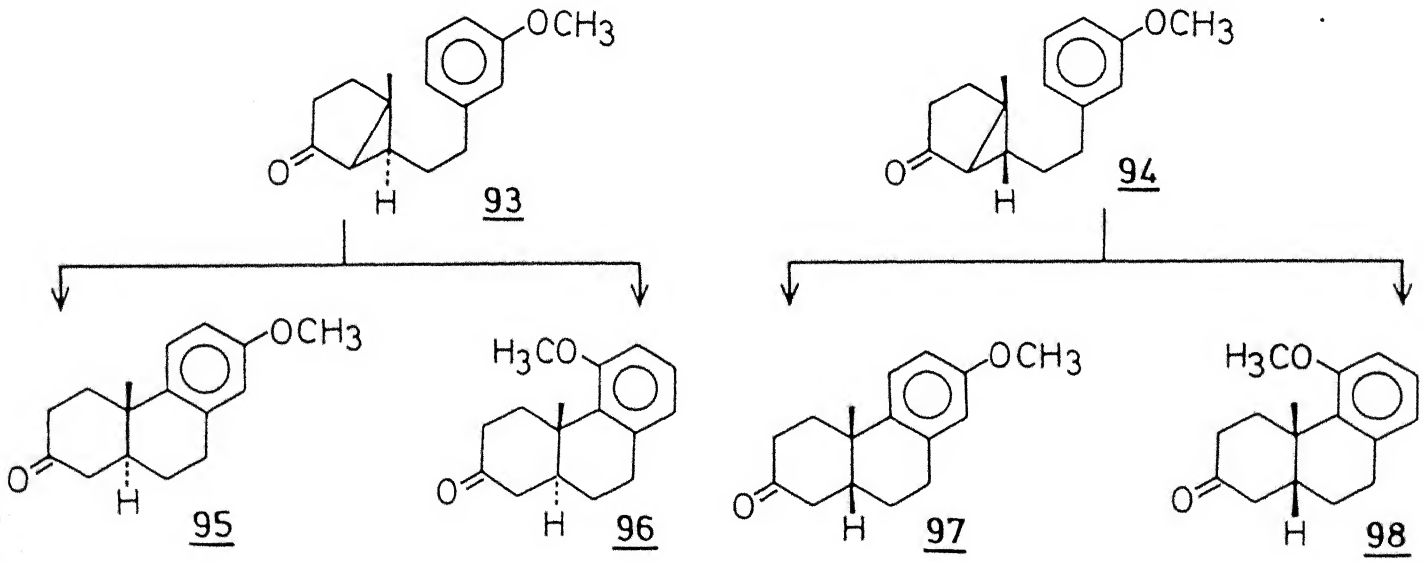


..(I.6)

Pittman and McManus[17] have shown that simple cyclopropyl ketones rearrange in conc. H_2SO_4 to the oxalan-2-ylium ions 88 which upon hydrolysis give γ-hydroxy ketones. The γ-hydroxy ketones could be oxidized to give 1,4-dicarbonyl compounds. Nakai et al.[18] have utilized the 1,4-dicarbonyl compound 89 generated from the cyclopropyl ketone 87 for the synthesis of the natural product dihydrojasmone (90) (Scheme I.45).

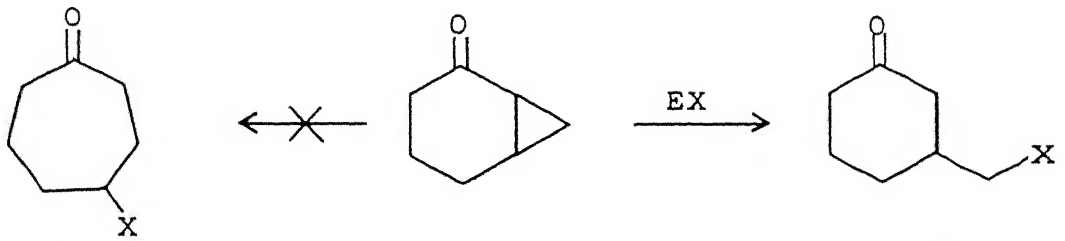


SCHEME I·46



SCHEME I 47

overlaps with the π orbitals of the carbonyl group. Thus with bicyclo[4,1,0]heptan-2-one 99 nucleophilic attack led to the formation of 100 and not the ring expanded product 101 (Scheme I.48).



101 99 100

SCHEME I.48

Several electrophilic reagent-nuclophile combinations have been used to open the cyclopropyl ketone systems. In the absence of an added nucleophile, the counterpart of the electrophilic reagents itself opens the cyclopropane ring. Various reagents reported in the literature as listed in Table I.1

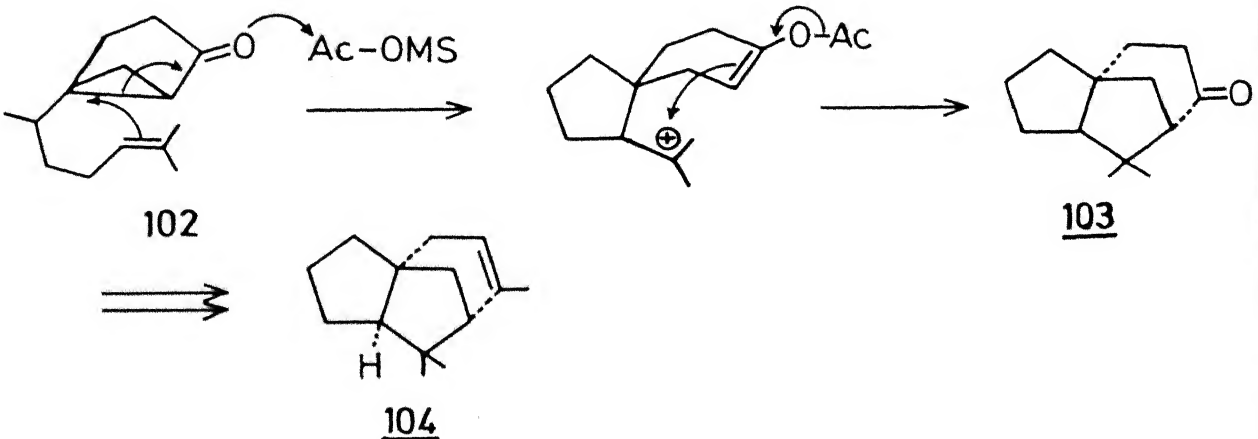
Table I.1

Sl. No.	Reagent	Nucleophile	Ref.
1.	AcOMS	I^-, Br^-, OMS	15
2.		Cl^-	21
3.	LiSePh	$PhSe^-$	22
4.	$SiMe_3I$	I^-	23
5.	$SiMe_3$-$OCOCF_3$	CF_3COO^-	24

The combination of acetylmethanesulphonate (AcOMS) and nucleophiles such as Br^- and I^- (derived from their

corresponding tetramethylammonium salts), gives regiospecific enol acetate, with a stereoselectivity of nucleophile addition which is compatible to S_N2 opening of the ring.[15] Corey et al.[25] have utilized this reagent for the intramolecular π-cation cyclization of the cyclopropyl ketone 102 , to give the key intermediate 103 for the stereoselective synthesis of the sesquiterpene cedrene (104) (Scheme I.49).

Pyridinium hydrochloride has been reported to give γ-chloroketones on reaction with cyclopropyl ketones.[21] Similarly, iodotrimethylsilane gives γ-iodoketones[23] and lithium phenylselenolate with cyclopropyl ketonesin refluxing benzene gives the γ-phenylselenides.[22]



102 103 104

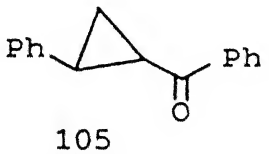
SCHEME I·49

I.B.2 Present Work

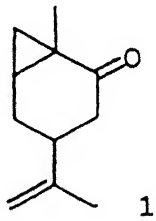
Generation of cyclopropyl carbinyl cation, the opening of cyclopropane ring, followed by an attack of a suitable nucleophile, appears to be an interesting pathway to form E- and Z-olefins stereoselectively. This has been discussed in the background part of this section, quoting examples from literature, where cyclopropyl carbinols were treated with different acids. Similarly cyclopropyl ketones (cf. Sec.I.B.1) could also be opened by means of an acid followed by nucleophilic attack (both in an inter- and intramolecular fashion) to lead to a variety of molecular frameworks.

Surprinsingly, there appears no example in the literature where the cyclopropyl ring of a cyclopropyl carbinol or cyclopropyl ketone has been opened by the nucleophilic attack of a nitrile. In the introduction part of this chapter, a mention has been made about the Ritter reaction taking place on a carbocation generated after this rearrangement of a spiroalcohol (Scheme I.6). But no report, as mentioned earlier (vide supra), appears of such a reaction on a cyclopropyl system. The present study was, therefore, undertaken to find out the behaviour of nitriles towards cyclopropyl ketones and cyclopropyl carbinols in the presence of an acid, i.e., typically under Ritter reaction conditions.

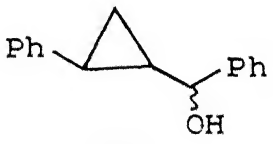
The substrates chosen for this study were the two cyclopropyl ketones, 2-phenyl benzoylcyclopropane (105) and the cyclopropyl ketone 106 generated from carvone, and the corresponding alcohols 107 and 108 obtained by their sodium borohydride reduction. Besides these, 2-phenyl cyclopropanemethanol (109) was also used for the study.



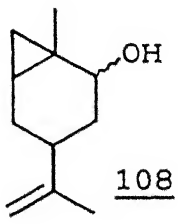
105



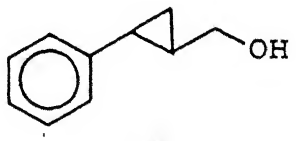
106



107



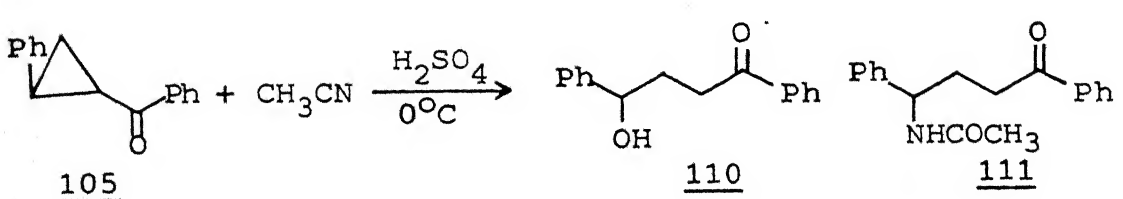
108



109

The cyclopropyl ketones 105 and 106 were prepared from their corresponding enones by following the literature[26] procedure using the ylid generated from trimethylsulphoxonium iodide.

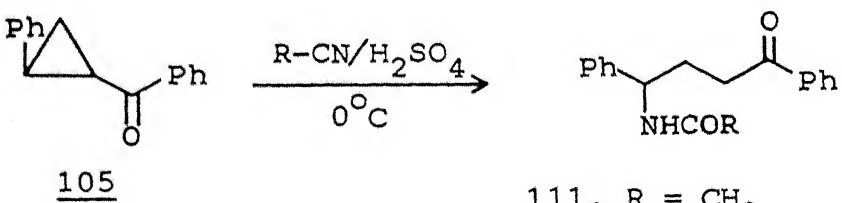
Initial studies, where the ketone 105 was taken in acetonitrile followed by addition of excess concentrated sulphuric acid at 0°C led to the exclusive formation of a γ-hydroxy ketone 110 (Eqn. I.7). No trace of the expected amide 111 was obtained



105 110 111 ..(I.7)

however. Similar results were obtained when the reaction was carried out with acrylonitrile and benzonitrile. The structure of the γ-hydroxy ketone 110 was confirmed by its spectral characteristics. Thus, its IR spectrum showed absorptions at 3310 cm^{-1} (br) and 1670 cm^{-1} (s) corresponding to ν(OH) and ν(C=O), respectively and ^{1}H NMR spectrum showed absorptions at δ 2.06-2.30 (m, 2H, $-C\underline{H}_2-OH$), 3.16 (t, 2H, J = 6 Hz, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_2$), 4.74 (br, t, 1H, J = 6 Hz, $-C\underline{H}-OH$), 6.96-7.88 (m, 10 H, Ar) and mass spectrum showed M^+ peak at 240.

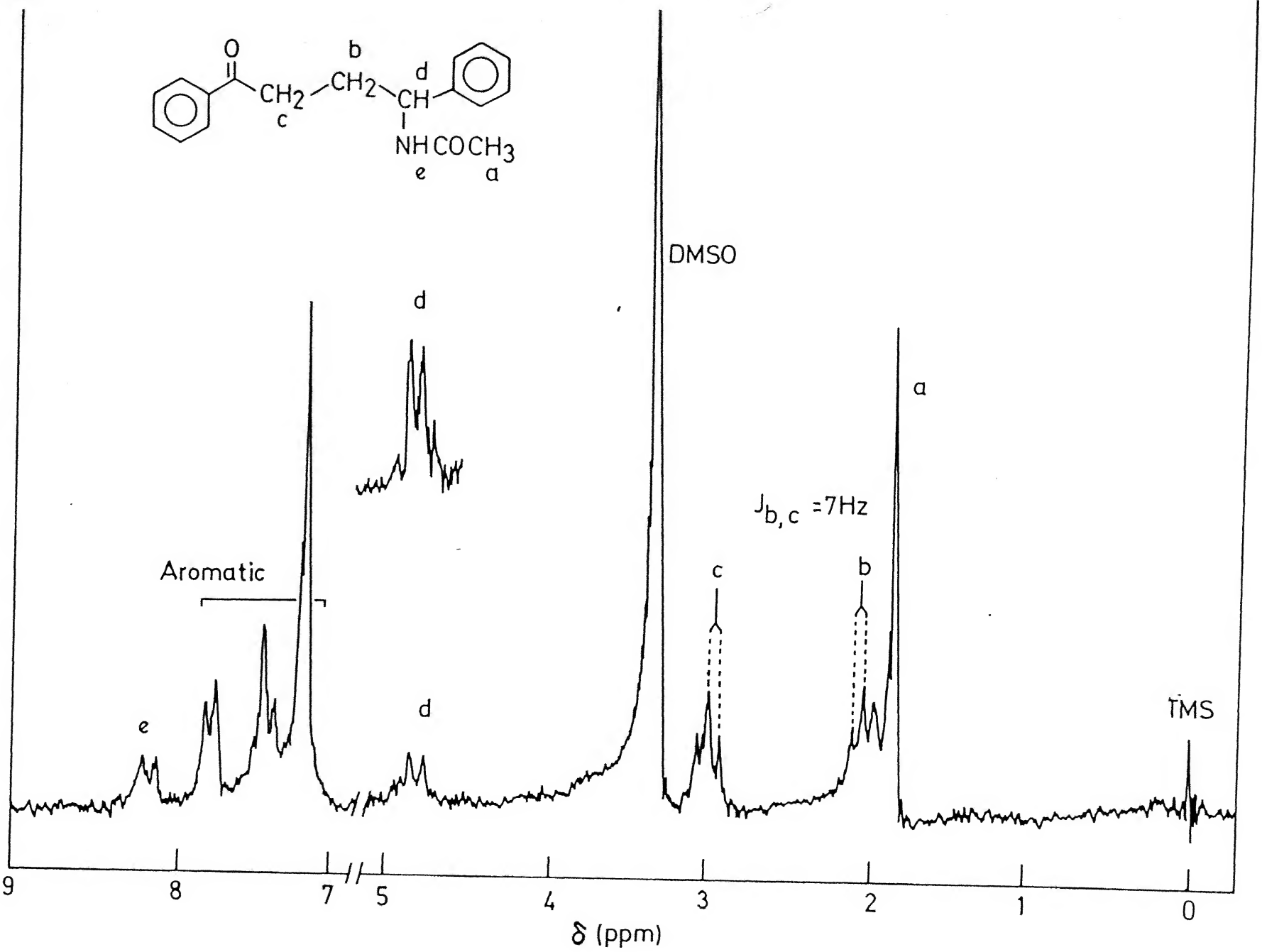
Proper experimental conditions were then found by us, wherein nitrile could be made to attack the cyclopropyl ketone. Thus, addition of acetonitrile to conc. sulphuric acid (4 molar equivalents with respect to cyclopropyl ketone) at 0°C, stirring for 30 minutes followed by the addition of the cyclopropyl ketone 105 and further reaction for 6 hrs. at 0°C gave the expected amide 111 in 64% yield (Eqn. I.8). Interestingly, no trace of the earlier formed γ-hydroxy ketone 110 was found to be present.



105

111, R = CH_3
112, R = CH_2=CH- .. (I.8)

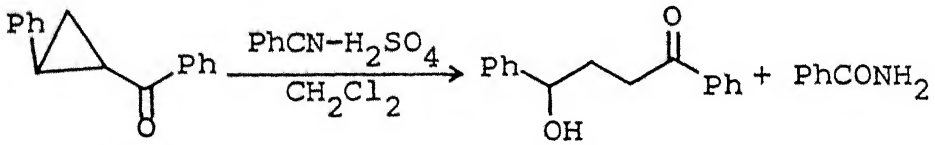
This amide 111 (m.p. 187°C) showed strong absorptions at 1640 cm^{-1} (ν_{CONH}), 1675 cm^{-1} ($\nu_{C=O}$) and 3260 cm^{-1} (ν_{N-H}) in its IR spectrum. ^{1}H NMR spectrum showed absorptions at δ 1.84 (s, 3H, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$), 1.88-2.2 (m, 2H, $-C\underline{H}_2-CH-Ph$), 3.02 (t, 2H, J = 6 Hz,


O
b
d
CH2
CH2
CH
c
NH CO CH3
e
a
DMSO
d
a
Aromatic
J b, c =7Hz
c
b
e
d
TMS
9
8
7
5
4
3
2
1
0
δ (ppm)

$-\overset{O}{\overset{\|}{C}}-C\underline{H}_2$), 4.68-4.92 (m, 1H, -NH-C<u>H</u>-), 7.08-7.98 (m, 10 H, aromatic), 8.2 (br, d, 1H, -N<u>H</u>-) and mass spectrum showed M^+ peak at 281. These data confirmed the structure of this amide <u>111</u>.

In a similar fashion, when acrylonitrile was used, the corresponding amide <u>112</u>, m.p. 189°C(d) was obtained in 55% yield which showed strong IR absorption bands at 1628 cm^{-1} ($\nu_{C=C}$), 1656 cm^{-1} (ν_{CONH}), 1679 cm^{-1} ($\nu_{C=O}$) and 3300 (ν_{N-H}). In ^1H NMR spectrum absorptions at δ 1.92-2.34 (m, 2H, -C<u>H</u>$_2$-), 3.02 (t, 2H, J = 6 Hz, $\overset{O}{\overset{\|}{C}}-C\underline{H}_2$), 4.8-5.12 (m, 1H, -NH-C<u>H</u>-), 5.4-6.46 (m, 3H, vinylic), 7.02-8.04 (m, 10 H, aryl) and 8.42 (br, d, 2H, -N<u>H</u>), were observed and mass spectrum showed M^+ peak at <u>293</u>. These data are in accordance with the structure assigned to the amide <u>112</u>.

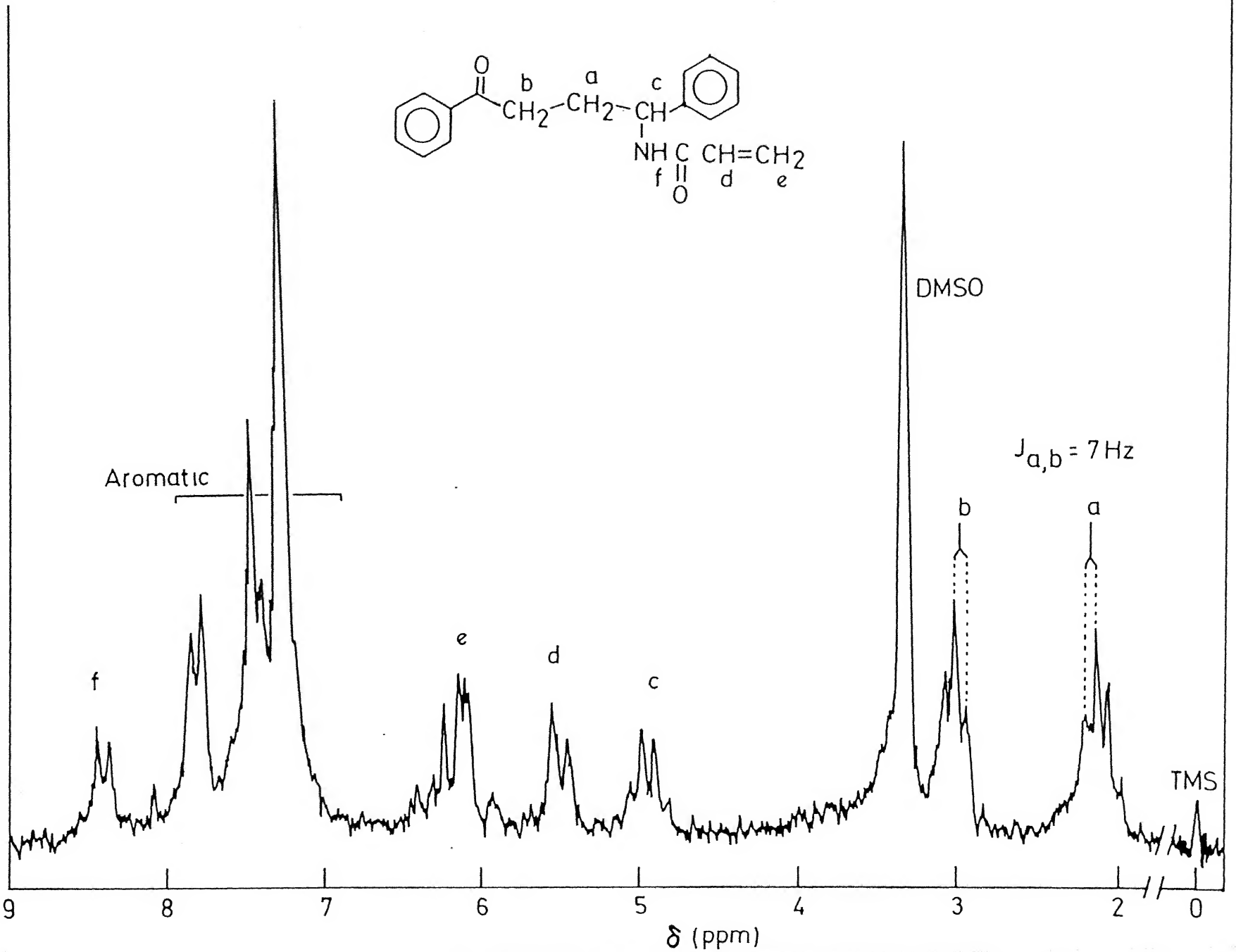
However, when the reaction was carried out using benzonitrile, dichloromethane had to be used as a cosolvent to avoid benzonitrile from freezing at 0°C. Surprisingly, in this case, under a variety of reaction conditions, only the γ-hydroxy ketone <u>110</u> was formed along with benzamide (Eqn. I.9). Since



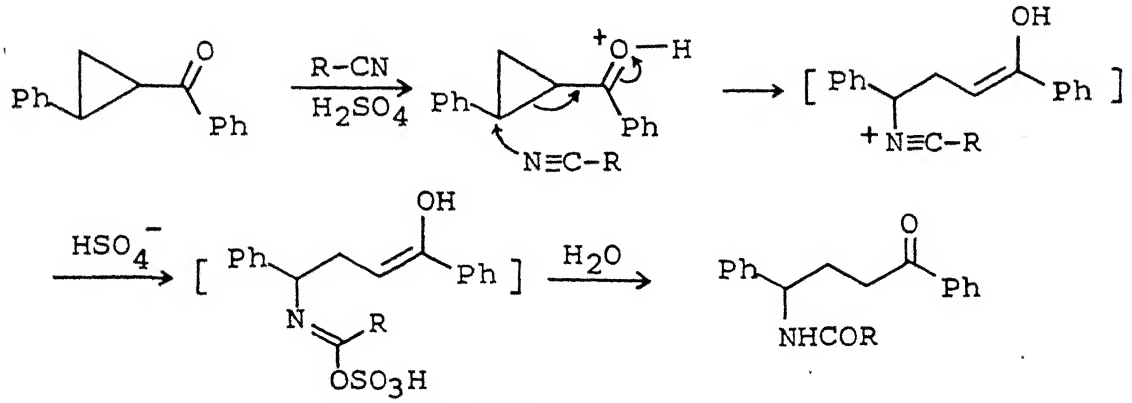
<u>105</u> <u>110</u> .. (I.9)

no Ritter reaction product was formed using benzonitrile, we concentrated our efforts in studying the reactions by using only these two nitriles, viz., acetonitrile and acrylonitrile.

The formation of the amides <u>111</u> and <u>112</u> from the cyclopropyl ketone <u>105</u> and nitrile in the presence of conc. H_2SO_4

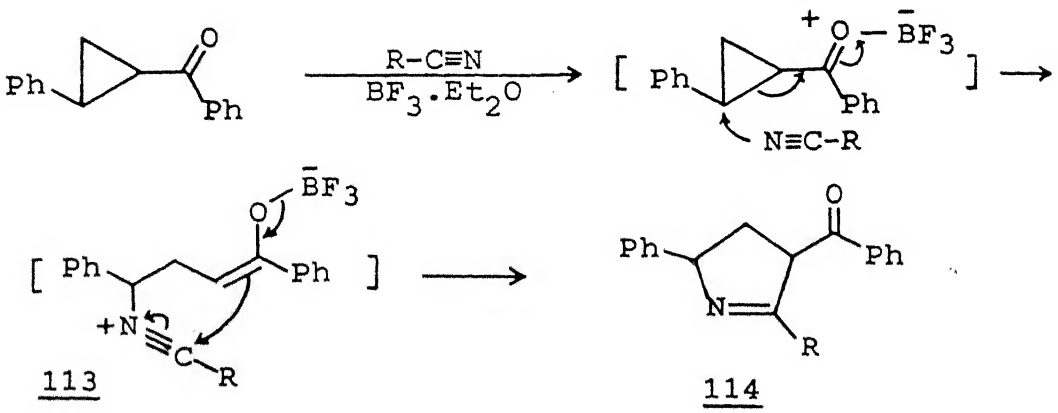

O
b
a
c
CH2–CH2–CH
NH C CH=CH2
f O d e
DMSO
Aromatic
Ja,b = 7 Hz
b
a
f
e
d
c
TMS
9
8
7
6
5
4
3
2
0
δ (ppm)

could be visualized as shown in Scheme I.50.



SCHEME I.50

We expected that if the reaction was carried out in the presence of a Lewis acid, where there would be no counterion present in the medium, then the intermediate such as 113 would undergo cyclization to give 114 (Scheme I.51). Thus, when the

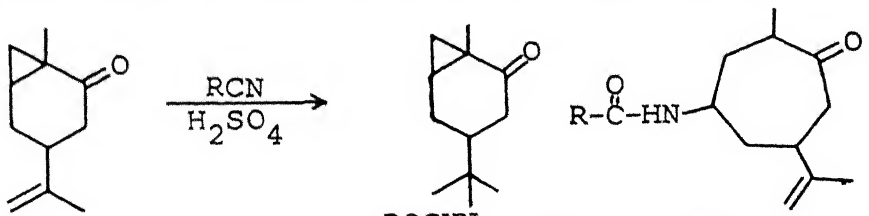


SCHEME I.51

ketone 105 was treated with acetonitrile or acrylonitrile in the presence of boron-trifluoride-etherate either in catalytic or in molar equivalent at 0°C, the disappearance of the starting

material was observed by monitoring with tlc. However, after complete reaction work-up and removal of the solvent, the tlc of the residue showed several products, indicating that the product(s) formed in the reaction were not stable. The product was observed to be fairly stable in a very dilute solution which quickly turned dark brown upon concentration. Owing to the fact these products were not isolable in pure form, it was not possible to characterize them.

We then turned our attention towards the other cyclopropyl ketone 106 derived from carvone. Thus, the ketone 106 upon treatment with a mixture of acetonitrile and conc. H_2SO_4 (1.5 equiv.) at 0^oC resulted in the formation of a single product (as shown by tlc). The IR spectrum of this compound 115 showed strong broad absorption bands at 1675 cm^{-1}, and 3340 cm^{-1}, and another band at 3440 cm^{-1}. Appearance of a single carbonyl group at 1675 cm^{-1} ruled out the possibility of an isolated carbonyl group, as might be expected by the opening of the cyclopropyl ring to form the compound 117 (Scheme I.52). The presence



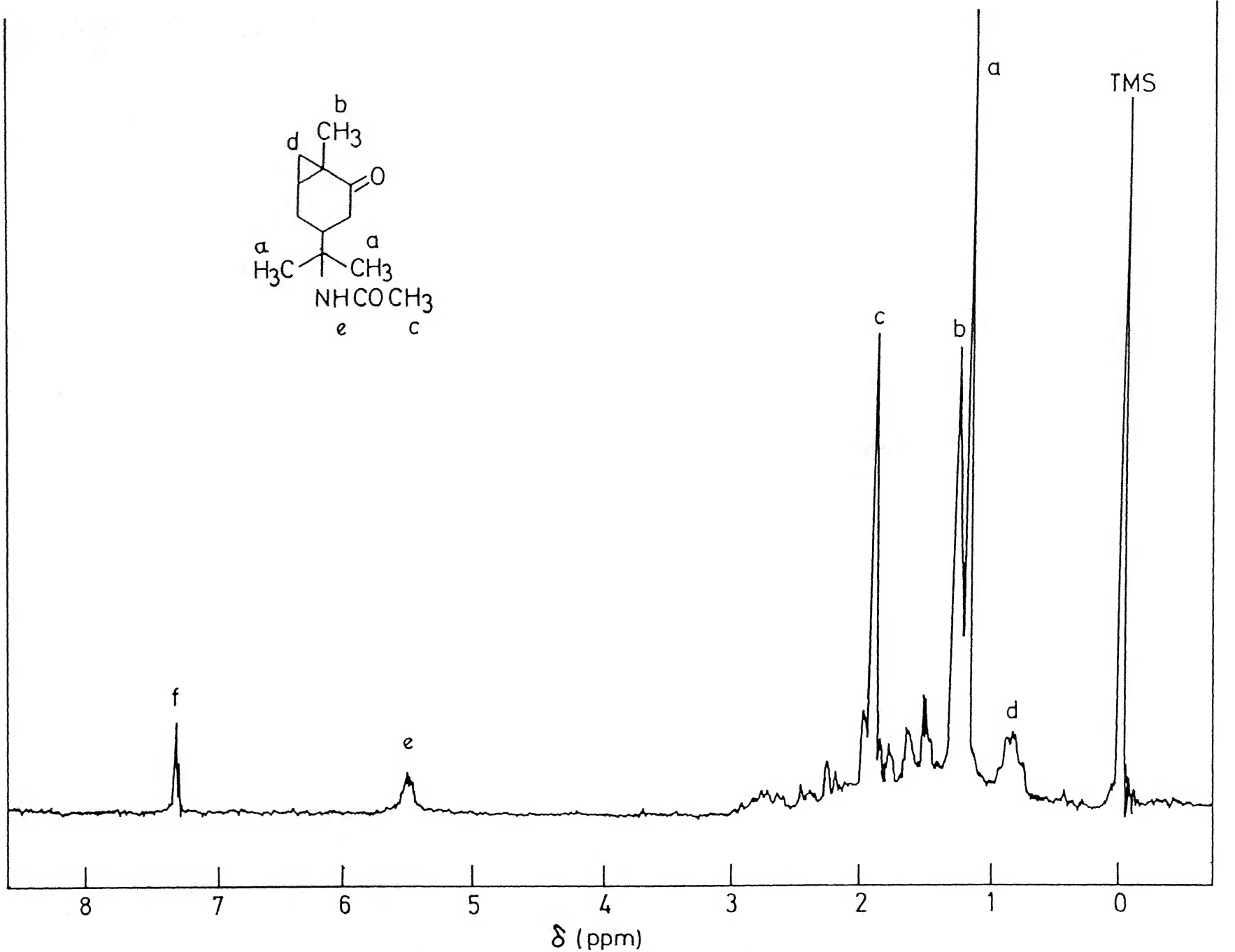
106

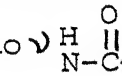
115, R = CH_3

116, R = $-CH=CH_2$

SCHEME I.52

of a weak band at 3050 cm^{-1} could be attributed to the presence

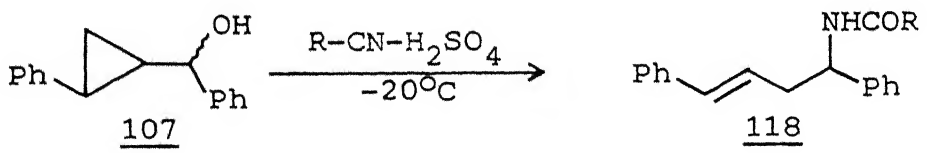

b
CH3
d
O
a
a
H3C
CH3
NHCOCH3
e
c
a
TMS
c
b
f
e
d
8
7
6
5
4
3
2
1
0
δ (ppm)

of cyclopropane ring. These observations were further augmented by ^{1}H NMR spectrum where the presence of a cyclopropane ring was apparent. ^{1}H NMR spectrum showed absorptions at δ 0.7-1.0 (m, 3H, H ), 1.17 (s, 6H, $(CH_3)_2$-C ), 1.27 (s, 3H, ), 1.87 (s, 3H, NH-C(=O)-CH_3) and 5.5 (br, s, 1H, N-H). The mass spectrum of this compound showed M^+ at 223. These spectral data clearly indicate the presence of a cyclopropane ring and disappearance of the olefinic moiety confirming the assigned structure 116, and ruling out the possibility of the expected structure 117. Its ^{13}C NMR spectrum also supported the structure assigned to it. (Full values of the ^{13}C NMR spectral data are reported in Sec. I.B.3). Under similar conditions, when the cyclopropyl ketone 106 was treated with acrylonitrile only one compound 116 was formed whose spectral data again indicated the presence of a cyclopropane ring system and disappearance of the olefinic moiety, thus confirming the structure assigned to it. In this case the IR spectrum showed two separate strong absorption bands at 1650 cm^{-1} and 1675 cm^{-1} corresponding to ν  and ν  (α-to cyclopropyl ring) and bands at 1622 cm^{-1} ($\nu_{C=C}$) and 3250 cm^{-1} (ν_{N-H}). A weak band at 3050 cm^{-1} could be attributed to the presence of a cycloprane ring. ^{1}H NMR spectrum showed absorption bands at δ 0.66-0.96 (m, 3H, H ), 1.18 (s, 6H, $(CH_3)_2$-C), 1.44-3.06 (m, 5H, two CH_2 and one H) and 5.36-6.34 (m, 4H, vinylic and one -N-H). The mass spectrum showed M^+ at 235. The ^{13}C NMR data (given in Sec. I.8.3) once again confirmed the structure 116 assigned to it.

This observation that cyclopropane ring is intact and the olefin undergoes reaction with the nitrile, indicates that the relative reactivity of an olefin under such conditions is higher than that of cyclopropyl ketones.

Next, we undertook the study of reactions of nitriles with the cyclopropyl carbinols 107, 108 and 109 under acidic conditions. For this purpose, the cyclopropyl ketones 105 and 106 were reduced with sodium borohydride to obtain the alcohols 107 and 108 in 99% and 89% yield, respectively. The carbinol 109 was prepared in 77 % yield by the Simmons Smith cyclopropanation of cinnamyl alcohol. Structures of these carbinols were confirmed by their spectral characteristics. Complete spectral data are reported in the experimental section (Sec. I.B.3).

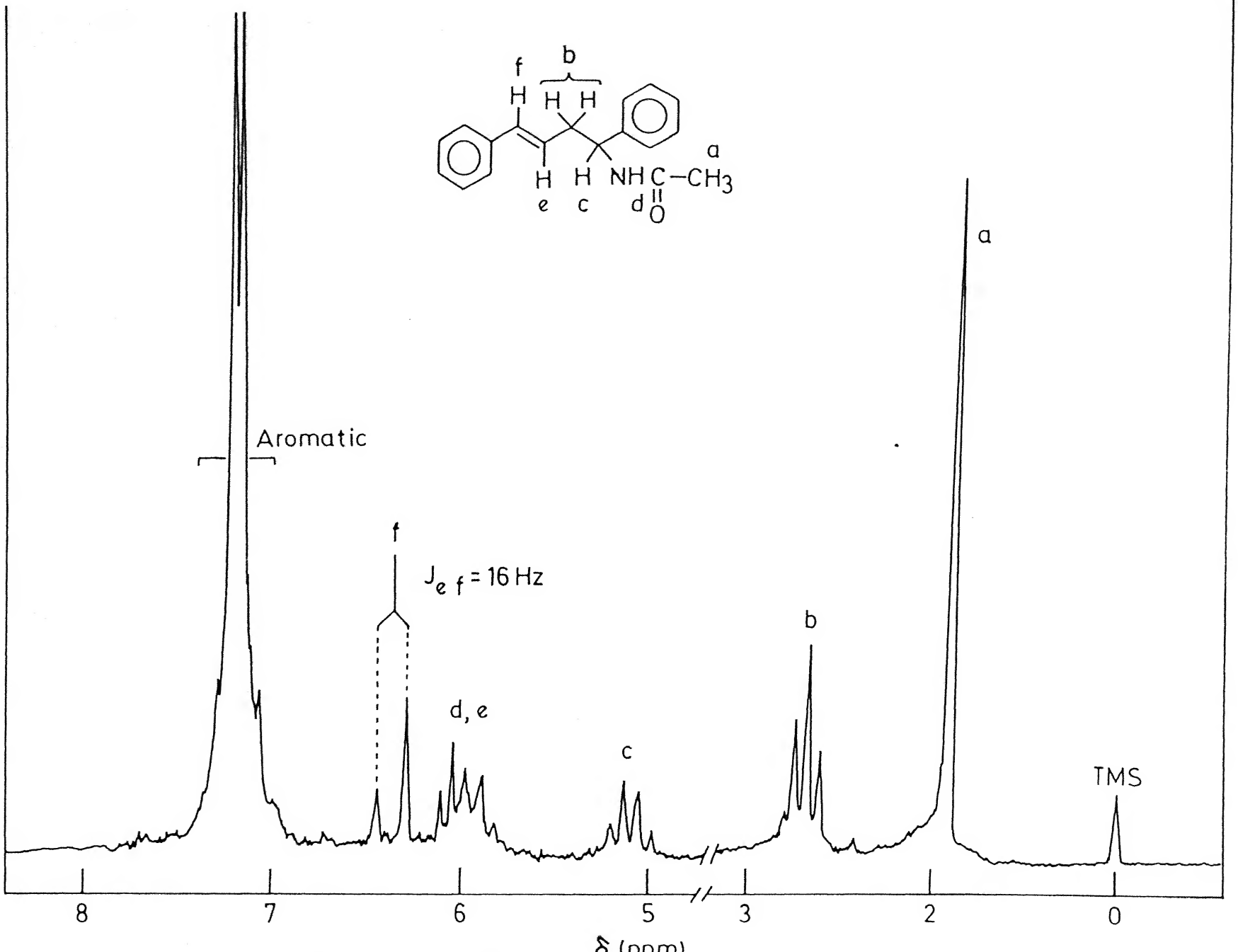
Treatment of acetonitrile with conc. H_2SO_4 at -20^oC followed by the addition of alcohol 107 led to the formation of a single product 118a (Eqn. I.10) in 66% yield whose structure was confirmed by its spectral characteristics. Thus, its IR spectrum showed absorptions at 1644 cm^{-1}, 1680 cm^{-1} and 3260 cm^{-1}



107 118

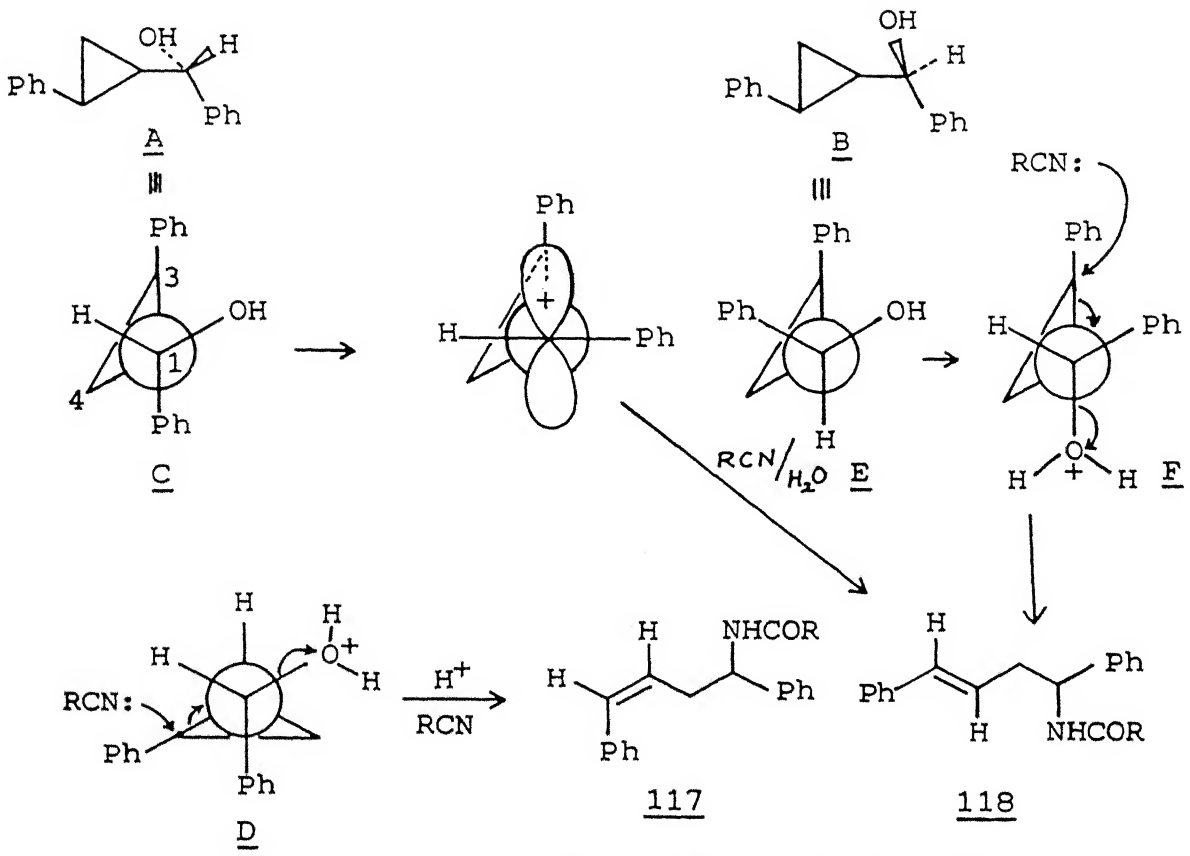
a, R = CH_3
b, R = $CH{=}CH_2$ ..(I.10)

corresponding to $\nu_{C=C}$, $\nu_{\overset{O}{\overset{\|}{C}}-NH}$ and ν_{N-H}. In its ^1H NMR spectrum absorptions at δ 1.92 (s, 3H, $NH-\overset{O}{\overset{\|}{C}}-CH_3$), 2.6-2.78 (t, 2H, allylic CH_2, J = 7 Hz), 4.94-5.22 (q, 1H, $-NH-\overset{O}{\overset{\|}{C}}-CH_3$), 5.68-6.48 (m, 2H,


f
b
H
H H
a
H H NH C–CH3
e c d O
Aromatic
f
$J_{e\,f}$ = 16 Hz
d, e
c
b
a
TMS
8
7
6
5
3
2
0
δ (ppm)

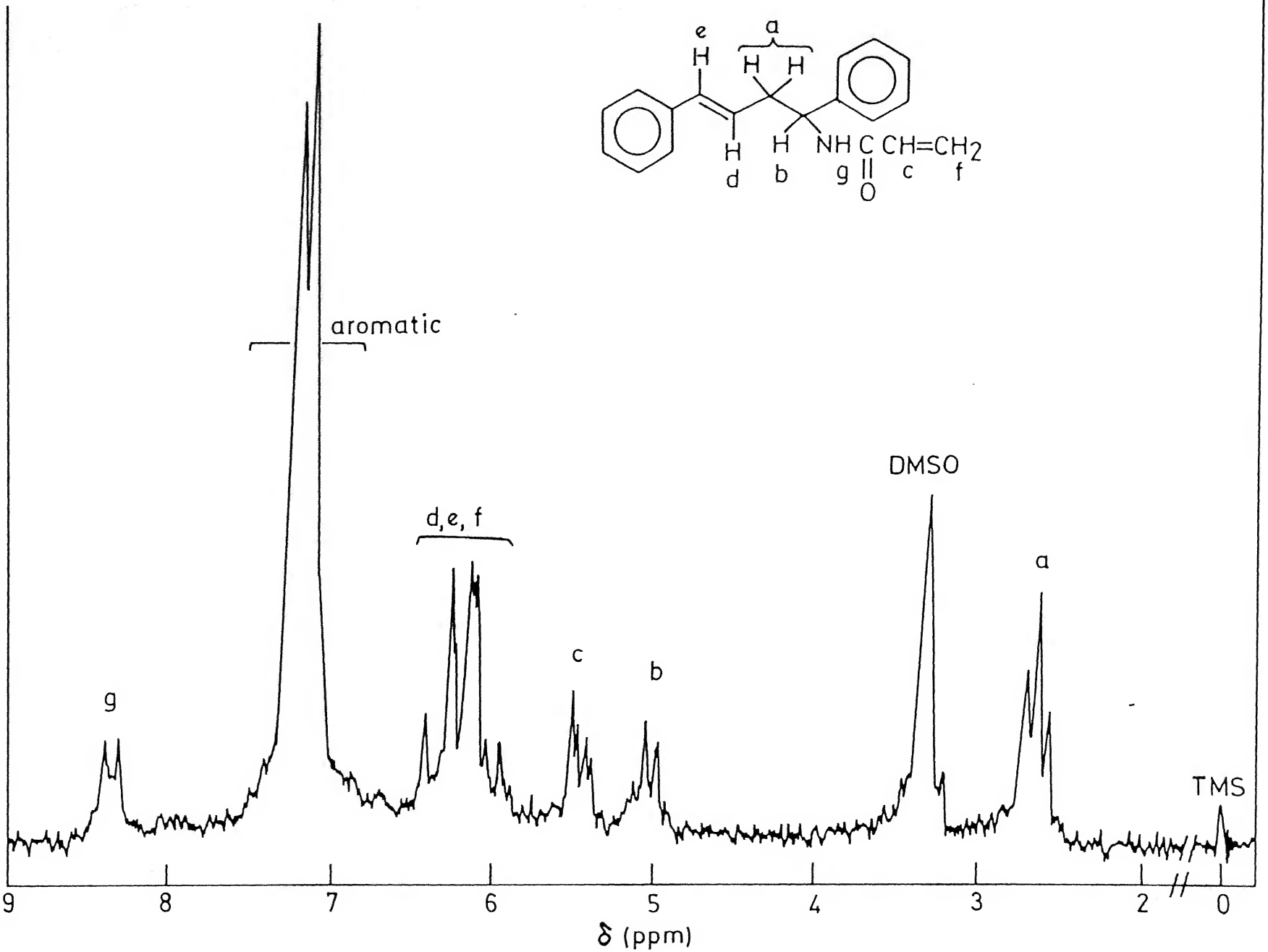
olefinic), 6.88-7.4 (m, 10 H, aromatic) were observed. Further its mass spectrum showed M^+ peak at 265.

The olefinic pattern in the ^1H NMR spectrum (Fig. I.9) of 118a indicates a clear doublet for proton H_f at 6.36δ with $J_{e,f}$= 16 Hz, which is a typical characteristic coupling constant for a trans olefin. It is also clear from this olefinic pattern that there is no contamination of any cis-product, which is further evident from the appearance of only one singlet for NH-$\overset{O}{\overset{\|}{C}}$-$CH_3$. The formation of only the trans product is interesting since the starting carbinol 107 is not a single stereoisomer as it has been obtained by the reduction with sodium borohydride which is not known to reduce stereospecifically. The two stereoisomers which could arise from the sodium borohydride reduction are A and B whose Newman projection formulae are C and E, respectively, as illustrated in Scheme I.53. It was not possible to separate the two isomers and hence the reaction was carried out on the mixture itself. From its ^1H NMR spectrum also it was not possible to determine the ratio of the two stereoisomers. According to the literature survey, as mentioned in the background part (cf. Scheme I.39), the opening of the cyclopropyl carbinol under acidic condition involves attack of the nucleophile in antiperiplanar fashion, i.e., the attack of the nucleophile, opening of the cyclopropane ring and departure of the leaving group are simultaneous. The formation of E-or Z-isomer is thus dependent upon a particular conformation as can be seen



SCHEME I.53

from its Newman projection formulae, having anti-periplanar arrangement. Also it has been observed that the ratio of E- and Z-isomer depends upon the relative stability of the conformations by considering anti-periplanar arrangement. Considering these factors one could expect the formation of a cis-product from the stereoisomer A and the trans-product from B. However, since only the trans product has resulted from the reaction, it is possible that the stereoisomer A does not assume the conformation D, which is sterically more strained (Ph and $\triangle$Ph being eclipsed), but assumes C, where such a strain


e
a
H
H H
H
H
H NH C CH=CH2
d
b
g
O
c
f
aromatic
d, e, f
c
b
DMSO
a
g
TMS
9
8
7
6
5
4
3
2
0
δ (ppm)

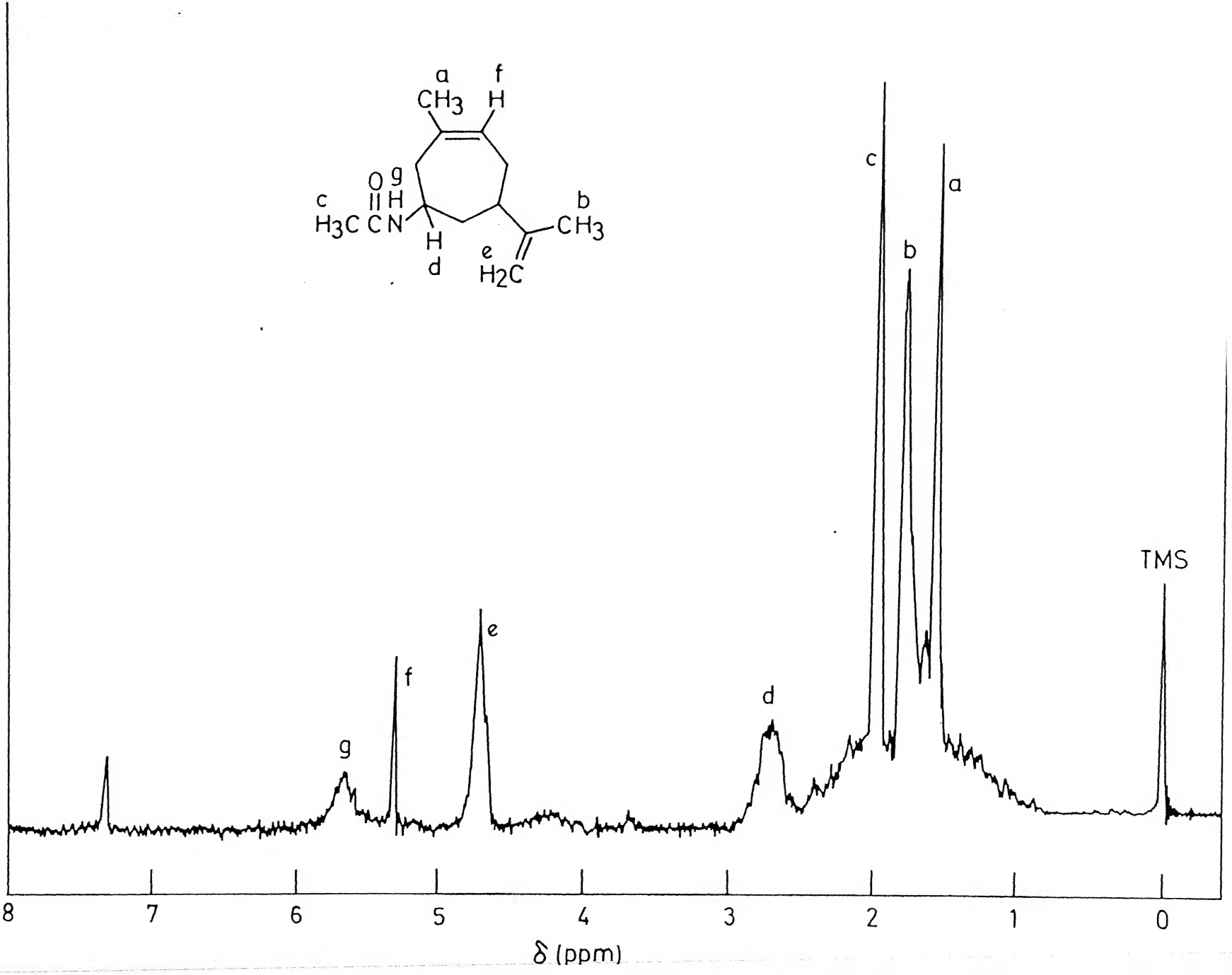
is less. Since the nucleophilicity of a nitrile is far less than e.g., Br^- (which has frequently been used by other workers) it is likely that the attack of the nitrile is somewhat slower than the departure of the leaving group. In assuming so we envision that the leaving group, i.e., protonated hydroxyl group first departs thereby generating a positive charge at C-1, i.e., it being now an sp^2 carbon atom, followed by opening of the cyclopropane ring and nucleophilic attack of the nitrile at C-3. This would lead to the formation of the thermodynamically more stable trans product from the isomer A. The isomer B, on the other hand, safely could assume the conformation F, which is strain free and also having anti-periplanar arrangement, and gives rise to the formation of the trans product. Thus, both the isomers A and B give the same product i.e., the E isomer 118.

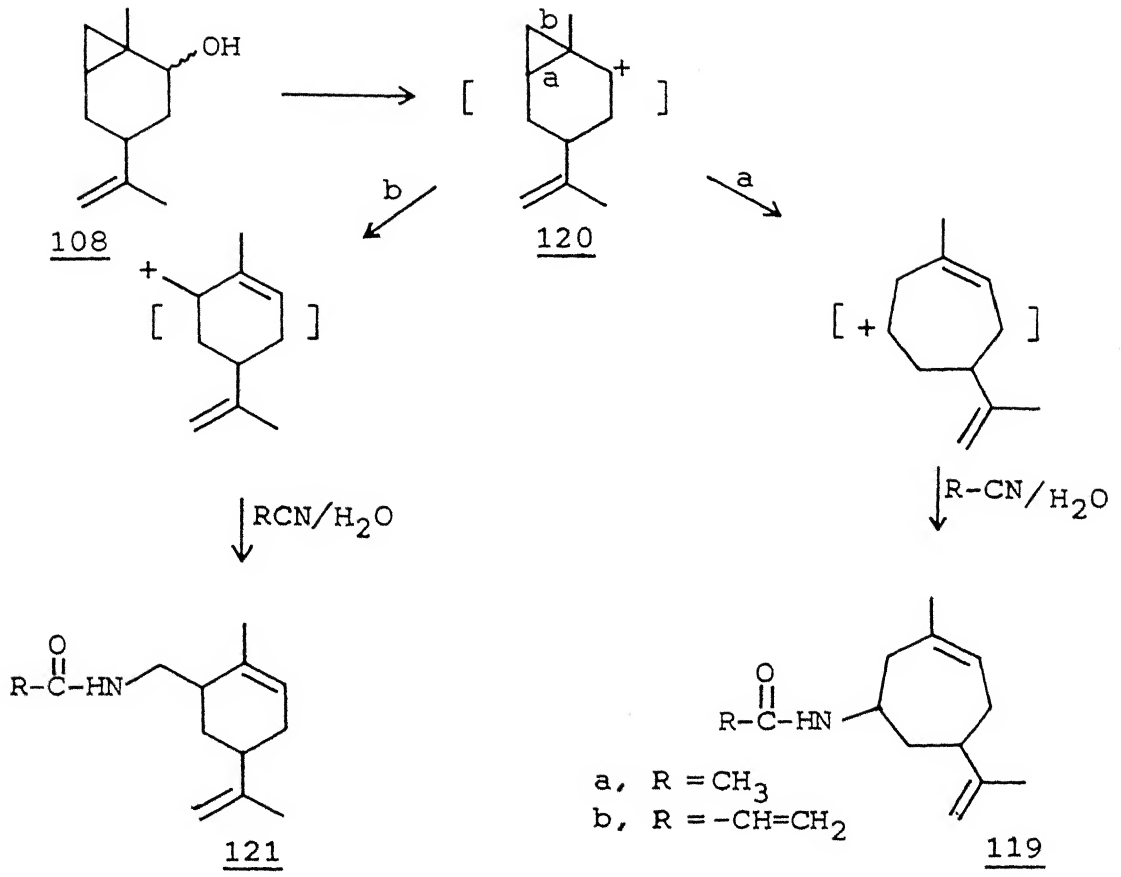
Repetition of similar experiment with carbinol 107 and acrylonitrile, instead of acetonitrile again led to the formation of only E isomer 118b as was evident from its spectral data (cf. Sec. I.B.3 for spectral data).

One again the typical trans olefinic pattern is clearly visible from the ^1H NMR spectrum (Fig. I.10) as the proton Ph-C<u>H</u>= appears as a doublet at δ6.34 with J = 15 Hz. Also there appears to be no cis product formed in this reaction since the spectral spectral pattern is almost similar to that of compound 118a.

In case of carbinol 108, a cyclic alcohol, treatment with acetonitrile in sulphuric acid medium underwent ring expansion leading to the formation of 119a in 35% yield (Scheme I.54). Spectral data for this compound as mentioned below are in complete agreement with this structure. IR ($CHCl_3$): 1655 (br, $\nu_{C=O}$, $\nu_{C=C}$) cm^{-1}, 3400 (ν_{N-H}). ^1H NMR ($CDCl_3$)δ(ppm): 1.5 (s, 3H, $H_3C\diagdown\!\!\diagup C=CH_2-$), 1.73 (s, 3H, $=\!\!\diagup\!\!\diagdown^{CH_3}_{CH-}$), 1.93 (s, 3H, $-NH-\overset{O}{\overset{\|}{C}}-CH_3$), 1.2-2.43 (m, 7H, $-CH_2-$ and allylic $-CH_2$) S and methines), 2.53-2.87 (m, 1H, -NH-CH-), 4.7 (br, s, 2H, $>=CH_2$), 5.27 (s, 1H, $=\!\!\diagup^{H}_{CH_3}$), 5.63 (br, s, 1H, -NH-).

The earlier observation, vide supra, that the reaction of acetonitrile with cyclopropyl ketone 106 occurred at the olefinic centre was not found in the presence case. Clearly the formation of a carbocation 120 from 108 (Scheme I.54), ring opening of the cyclopropane ring followed by attack of the nitrile is the course of this reaction. Out of the two bonds of cyclopropane ring viz., a and b the opening of a would lead to the formation of a seven-membered ring compound 119a whereas opening of b would lead to the formation of a six-membered ring compound 121. The fact that the ^1H NMR spectrum of the product shows a multiplet of one proton intensity for -N-CH- at δ (2.53-2.87) is a clear indication of the formation of 119 rather than 121. This is further augmented by its ^{13}C NMR spectrum, where a doublet for -N-C-H (a methine) is observed at 45.9 in its proton coupled spectrum. Such a ring expansion of a bicyclic system with one ring being cyclopropyl has been observed by

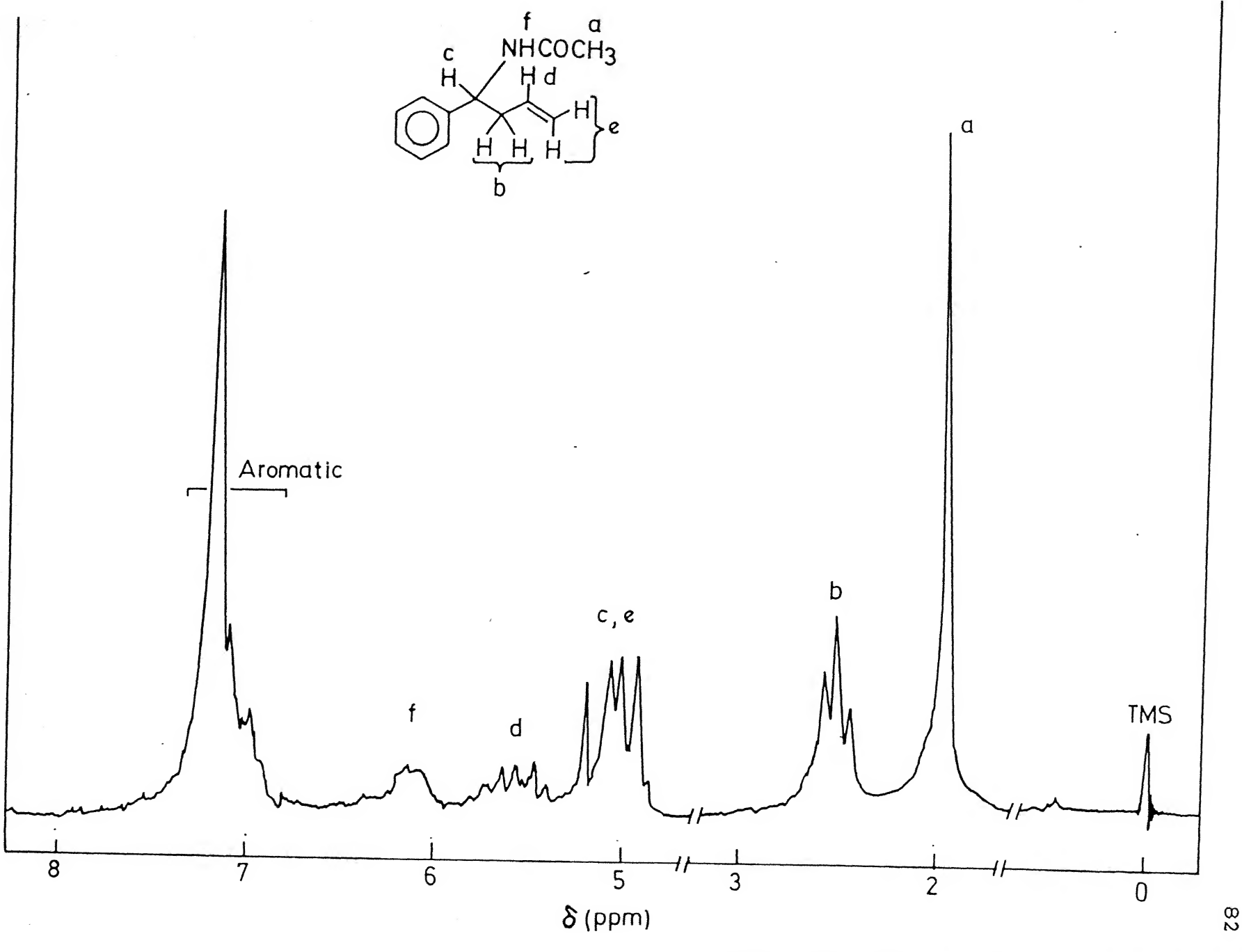

a
f
CH3
H
O
g
H
c
H3C C N
H
d
b
CH3
e
H2C
c
a
b
TMS
e
f
g
d
8
7
6
5
4
3
2
1
0
δ (ppm)



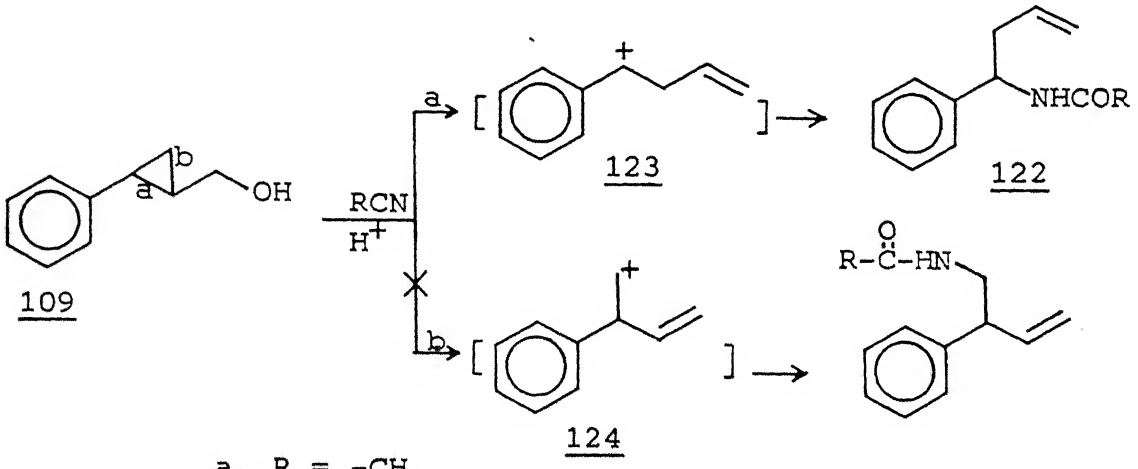
SCHEME I.54

Stork et al.[11] and it has been mentioned in the background part of this chapter. Apparently the p orbital of the carbonium ion has a better overlap with 'a' bond orbital than with 'b' bond orbital as rationalised by Stork et al.[19] and hence the ring expansion is preferred.

Use of acrylonitrile in place of acetonitrile also led to the formation of a seven membered ring amide 119b whose structure was again in conformity with its spectral data. These data are mentioned in the experimental section (I.B.3).


f
a
NHCOCH3
c
H
H d
H
e
H H H
b
a
Aromatic
b
c, e
f
d
TMS
8
7
6
5
3
2
0
δ (ppm)

Finally we have studied the reaction of cyclopropyl alcohol 109 with acetonitrile and acrylonitrile under similar conditions as mentioned above. Thus, when acetonitrile was reacted with 109, the product 122a (Scheme I.55), as expected, was formed in 58% yield. Its spectral data as mentioned below



109 123 122 124

a, R = $-CH_3$

b, R = $-CH=CH_2$

SCHEME I.55

are in complete agreement with the structure assigned to it. IR ($CHCl_3$): 1675 (ν_{C-NH}) cm^{-1}, 3420 (ν_{N-H}) cm^{-1}. ^1H NMR ($CDCl_3$) (ppm): δ 1.96 (s, 3H, $-N-C-CH_3$), 1.66-1.92 (m, 2H, allylic CH_2), 2.54 (t, 1H, CH-NH, J = 7 Hz), 4.84-5.78 (m, 3H, olefinic), 6.84-7.44 (m, 5H, aromatic). Mass spectrum, m/e (rel. ab.): 189 (M^+).

Once again out of the two possibilities of cyclopropane ring opening i.e., by breaking bond a or b (Scheme I.55, path a and b), a cleavage seems to be taking place. This is apparent from the NMR spectral data as the proton NH-CH appears as a broad triplet of one proton intensity at δ 2.54. Besides this, the allylic proton also appears as a multiplet of two proton

intensity at δ 1.66-1.92. Preference of cleavage of bond a is expected since it leads to the intermediacy of more stable carbocation 123 than 124.

As studied in other cases, this reaction was also carried out by using acrylonitrile and once again only one product viz., 122b was formed in 64% yield. The spectral data for this compound, as mentioned in Sec. I.B.3, confirmed its structure.

This study of the opening of cyclopropyl alcohols, under acidic conditions with nitriles as nucleophiles, has no precedence in literature. From this study, it is clear that the direction of ring opening is dependent upon the stability of the intermediates viz., the carbocations. In addition, consideration of the stability of the Newman projection formulae for the anti-perplanar arrangement in acyclic cases and the overlap of the p orbital of the carbonium ion with the cyclopropyl bond in cyclic cases seems to be important.

I.B.3 Experimental

The details of the instruments used are the same as described in Section I.A.3. ^{13}C NMR spectra were recorded on NT-200 Nicolet (200 MHz) spectrometer. The solvents used were dried in the same manner as described in Sec. I.A.3.

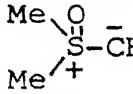
Chalcone was prepared by condensation of benzaldehyde and acetophenone.[27] Carvone and cinnamyl alcohol used were procured from Aldrich Chemical Co. The concentrated sulphuric acid used in the reactions was purchased from Ranbaxy and was 98% pure (AR grade).

Preparation of Trimethylsulphoxonium Iodide

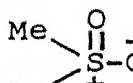
A solution of dimethylsulphoxide (DMSO) (9.6 g, 0.123 mol) and 18.0 ml of methyl iodide was refluxed under nitrogen atmosphere for 3 days. The precipitated solid was filtered and washed with chloroform. It was then dried and recrystallized from water to give colourless prisms of the sulphoxonium salt; yield, 14.0 g (52%).

Preparation of 2-Phenyl benzoylcyclopropane (105)

0.77 g (0.016 mol) of sodium hydride (50% dispersion in mineral oil) was placed in a three neck round bottom flask, and washed thrice with light petroleum ether (to remove the oil) and

evacuated till petroleum ether was removed (under N_2 atmosphere). Then 3.53 g (0.016 mol) of powdered trimethylsulphoxonium iodide was introduced under dry N_2 atmosphere, followed by the addition of 17.5 ml of dry DMSO via syringe. The reaction mixture was stirred using a mechanical stirrer for about 20 minutes (till evolution of H_2 ceased) to give milky white reaction mixture containing the ylid, i.e.,  , which was cooled to 10°C and 3.12 g (0.015 mol) of chalcone in 7.5 ml DMSO was slowly introduced during 15 min. The reaction mixture was brought to room temperature and stirred for 3 hr and then poured into 60 ml of ice cold water, extracted with ether (3 x 25 ml), washed twice with water and brine and then dried over anhyd. Na_2SO_4. Evaporation of the solvent on rotary evaporator followed by recrystallizing the oily residue from petroleum ether (40-60°) gave 3.1 g (93%) of 105, m.p. 47-49°C (lit.[26] 45.5-50°C).

Preparation of 1-Methyl-2-oxo-4-(1-methylethenyl)bicyclo[4.1.0]-heptane (106)

A solution of the ylid,  , was prepared as described in the previous experiment using 0.67 g (0.014 mol) of sodium hydride, 3.08 g (0.014 mol) of the oxo-sulphonium salt and 16.5 ml dry DMSO. A solution of freshly distilled carvone (2.0 g, 0.013 mol) in 3.5 ml DMSO was added at about 10°C. The reaction was then stirred for 2 hr at 0°C and then at 50°C for 1 hr. It was then poured into 6.0 ml of cold water, and worked up by extracting with ether (3 x 25 ml), washed twice with water and brine

and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product whose distillation under vacuum gave 1.92 g (88%) of 106, b.p. 110°C/10 mm (lit.[26] 109-110°C/ 10 mm).

Reaction of 2-Phenyl benzoylcyclopropane with conc. H_2SO_4 in Acetonitrile: Formation of 1-Phenyl-3-benzoylpropanol (110)

To a solution of 0.400 g (1.8 mmol) of the cyclopropyl ketone 105 in 1.0 ml acetonitrile at 0°C, was slowly added 1.0 ml (18.4 mmol) of conc. H_2SO_4 in about 30 mins. time. The reaction mixture was stirred for 12 hr at 0°C (disappearance of starting material on tlc was observed), and then poured into about 10 g of crushed ice and neutralized with 10% aq. NaOH solution. Extraction with ethyl acetate (3 x 15 ml), drying with anhydrous sodium sulphate, followed by evaporation of the solvent, and recrystallization of the crude solid from ethanol gave white crystals of 110, m.p. 100-101°C (lit.[28] m.p. 101°C) (yield, 0.362 g, 84%).

IR (KBr), ν_{max} (cm^{-1}): 1670 ($\nu_{C=O}$), 3310 (br, ν_{O-H}).

PMR ($CDCl_3$), δ (ppm): 2.06-2.30 (m, 2H, $C\underline{H}_2$-CHOH); 3.16 (t, 2H, J = 6 Hz, -CO-$C\underline{H}_2$), 4.74 (br, t, 1H, J = 6 Hz, $C\underline{H}$-OH), 6.96-7.88 (m, 10 H, aromatic).

Mass spectrum, m/e (rel. ab.): 240 (16, M^+), 222 (22, M^+-H_2O), 133 (28, M^+-Ph-CH-OH), 120 (100, M^+-Ph-CO-CH_3), 105 (62), 77 (45.).

Reaction of 2-Phenylbenzoylcyclopropane with Acetonitrile: Formation of N-(α-phenyl-β-phenacyl)ethyl acetamide (111)

To 0.22 ml (4.0 mmol) of conc. H_2SO_4 at 0°C was added slowly in about 20 min. 1 ml of acetonitrile and stirred for 30 min. A solution of 222 mg (1.0 mmol) of the cyclopropyl ketone 105 in 1.0 ml acetonitrile was then introduced slowly during 30 mins. time. After 6 hr of stirring at 0°C, the reaction mixture was poured out 15 g of crushed ice and neutralized with 10% aqueous NaOH solution. Extraction with ethyl acetate (3 x 15 ml), drying the extract with anhyd. Na_2SO_4 and evaporation of the solvent gave a crude solid, which on recrystallization with ethyl acetate-ether mixture gave white fluffy crystals of 111, m.p. 187°C (yield, 0.117 g, 64%).

IR (KBr), ν_{max} (cm^{-1}): 1640 (ν_{CONH}), 1675 ($\nu_{C=O}$), 3260 (ν_{N-H}).

PMR (DMSO, D_6), δ (ppm): 1.84 (s, 3H, $COCH_3$), 1.88-2.2 (m, 2H, $-CH_2-CHPh$), 3.02 (t, 2H, J = 6 Hz, $COCH_2-$), 4.68-4.92 (m, 1H, NH-CH-), 7.08-7.98 (m, 10 H, aromatic), 8.2 (br, d, 1H, -NH).

Mass spectrum, m/e (rel. ab.): 281 (35, M^+), 248 (65, M^+-COCH_3), 162 (35, $M^+-PhCOCH_2$), 161 (13, $M^+-PhCOCH_3$), 120 (50), 106 (100), 105 (35), 77 (28).

Anal. for $C_{18}H_{19}NO_2$, Calcd.: C, 76.87; H, 6.76; N, 4.98.
Found : C, 76.54; H, 6.52; N, 4.79%.

Reaction of 2-Phenylbenzoyl cyclopropane with Acrylonitrile: Formation of N-(α-phenyl-β-phenacyl)ethyl propenamide (112)

The reaction was carried out in the same manner as in the earlier procedure, on the same scale, using acrylonitrile in place of acetonitrile and a reaction time of 5 hr at 0°C. The crude product, obtained after work-up, was recrystallized from ethyl acetate-dichloromethane-petroleum ether (60-80°C) mixture to give white crystals of the amide 112, m.p. 189°C(d) (yield: 0.16 55%).

IR (KBr), ν_{max} (cm^{-1}): 1628 ($\nu_{C=C}$), 1656 (ν_{CO-NH}), 1679 ($\nu_{C=O}$), 3300 (ν_{NH}).

PMR (DMSO-D_6), δ (ppm): 1.92-2.34 (m, 2H, -C<u>H</u>$_2$-CHN), 3.02 (t, 2H, J = 6 Hz, COC<u>H</u>$_2$), 4.8-5.12 (m, 1H, NH-C<u>H</u>-), 4.5-6.46 (m, 3H, vinylic), 7.02-8.04 (m, 10 H, aromatic) and 8.42 (br,d, 1H, -N<u>H</u>-).

Mass spectrum, m/e (rel. ab.): 293 (35, M^+), 238 (63, M^+, $COCH=CH_2$), 222 (35, $M^+-CH_2=CH-CONH_2$), 174 (43, $M^+-PhCOCH_2$), 160 (48), 120 (45), 106 (100), 105 (45), 77 (40).

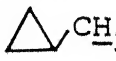
Anal. for $C_{19}H_{19}NO_2$, Calcd.: C, 77.81; H, 6.48; N, 4.78.
Found : C, 77.75; H, 6.52; N, 4.58%.

Reaction of Cyclopropyl Ketone (106) with Acetonitrile: Formation of the Amide (115)

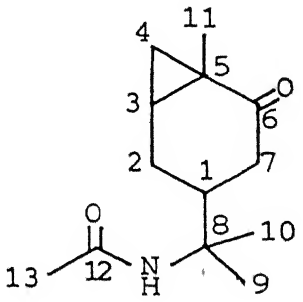
To 0.05 ml (0.92 mmol) of conc. H_2SO_4 was added slowly with stirring 0.5 ml of acetonitrile at 0°C during 15 minutes. After

30 min of stirring, a solution of the cyclopropyl ketone 106 (0.10 g, 0.61 mmol) in 0.5 ml acetonitrile was introduced during 15 minutes time. The reaction mixture was stirred for 7 hr at 0°C and then poured over 5 g of crushed ice, neutralized with 10% aq. NaOH and extracted with ethyl acetate. Evaporation of solvent, after drying with anhyd. Na_2SO_4, gave the crude product which on separation by thick layer chromatography (silica gel) using benzene-acetone, 8:2 as eluent gave the amide 115 as a thick liquid (yield: 0.076 g, 56%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1675 (br, $\nu_{C=O}$ and ν_{CONH}) 3340 (br, ν_{N-H}), 3400 (ν_{NH}).

PMR ($CDCl_3$), δ (ppm): 0.7 - 1.0 (m, 3H, ), 1.7 (s, 6H, $(C\underline{H}_3)_2C$), 1.27 (s, 3H, ), 1.87 (s, 3H,), 5.5 (br, s, 1H, N-H).

^{13}C NMR ($CDCl_3$), δ (ppm): C_1, 34.5; C_2, 22.6; C_3, 25.8; C_4, 17.2; C_5, 29.5; C_6, 210.7; C_7, 38.1; C_8, 55.7; C_9, 24.3; C_{10}, 23.8; C_{11}, 19.4; C_{12}, 24.3; C_{13}, 169.4.



Mass spectrum, m/e (rel. ab.): 223 (8, M^+), 164 (38, M^+-$-NH_2COCH_3$), 149(8), 121 (15), 100 (100), 58 (100).

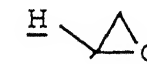
Anal. for $C_{13}H_{21}NO_2$, Calcd.: C, 69.96; H, 9.42; N, 6.28.
Found : C, 69.69; H, 9.50; N, 6.39%.

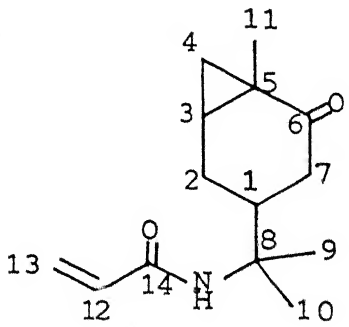
Reaction of (106) with Acrylonitrile: Formation of the Amide (116)

By using acrylonitrile in place of acetonitrile, the above reaction of 106 with conc. H_2SO_4, on the same scale but with a

reaction time of 10 hr at 0°C, was repeated. After work-up and thick layer chromatographic separation a solid compound was obtained, which was recrystallized from chloroform-petroleum ether to give the crystalline amide 116, m.p. 107-108°C (yield: 0.079 g, 55%).

IR (KBr), ν_{max} (cm^{-1}): 1622 ($\nu_{C=C}$), 1650 (ν_{CONH}), 1675 ($\nu_{C=O}$), 3250 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 0.66-0.96 (m, 3H, ), 1.18 (s, 6H, $(C\underline{H}_3)_2$-$\overset{|}{\underset{|}{C}}$-), 1.44-3.06 (m, 5H, two CH_2's and one -C-H), 5.36-6.34 (m, 4H, vinylic 3 and N-H).



^{13}C NMR ($CDCl_3$), δ (ppm): C_1, 34.7; C_2, 22.6; C_3, 25.8; C_4, 17.2; C_5, 29.5; C_6, 210.7; C_7, 38.1; C_8, 55.9; C_9, 24.3; C_{10}, 23.8; C_{11}, 19.3; C_{12}, 131.4; C_{13}, 126.0; C_{14}, 164.6.

Mass spectrum, m/e (rel. ab.): 235 (10, M^+), 164 (20, M^+-H_2N-$\overset{O}{\overset{\|}{C}}$-CH=$CH_2$), 149 (5), 120 (10), 112 (70), 58 (100), 54 (37).

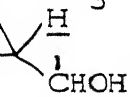
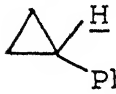
Anal. for $C_{14}H_{21}NO_2$, Calcd.: C, 71.49; H, 8.94; N, 5.96.
Found : C, 71.31; H, 8.78; N, 5.86%.

Reduction of 2-Phenylbenzoylcyclopropane (105) to (α,2-diphenyl) cyclopropane Methanol (107)

To a solution of 1.0 g (4.5 mmol) of the cyclopropyl ketone 105 in 15 ml methanol at 0°C, was added slowly 0.19 g (5.0 mmol) of solid sodium borohydride. The reaction mixture was stirred for 30 min. at 0°C and then methanol removed under reduced pressure. The residue was dissolved in dichloromethane (about 25 ml),

washed once with water, brine and then dried over anhydrous sodium sulphate. Removal of solvent gave the cyclopropyl carbinol 107 as a gum (yield: 0.998 g, 99%).

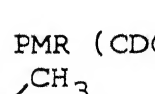
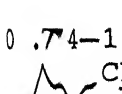
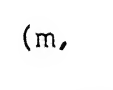
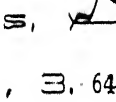
IR (thin film), ν_{max} (cm^{-1}): 1615 (ν_{C-C} (△)), 3400 (ν_{O-H}).

PMR ($CDCl_3$), δ(ppm): 0.72–1.16 (m, 2H, $\underline{H}_2C$△), 1.24-1.60 (m, 1H, ), 1.80-2.10 (m, 1H, ), 2.24 (s, 1H, -O$\underline{H}$), 4.12 & 4.22 (2d, 1H, J=7 & 6 Hz-C$\underline{H}$-OH), 6.68-7.54 (m, 10 H, aryl).

Reduction of 106 to 1-Methyl-2-hydroxy-4(1-methylethenyl)-bicyclo-[4.1.0]heptane (108)

To a solution of 400 mg (2.45 mmol) of the cyclopropyl ketone 106 in 5 ml methanol at 0°C was added 0.19 g (4.9 mmol) of solid sodium borohydride. After 30 min., the reaction mixture was brought to room temperature and stirred for additional 10 hr. Work-up as described in the earlier case (cf. reduction of 2-phenylbenzoylcyclopropane) gave the crude product, which was purified by a bulb to bulb distillation set-up, at 80°C (oil-bath temperature) and 1 mm pressure, to give the cyclopropyl-carbinol 108, (yield: 0.360 g, 89%).

IR (thin film), ν_{max} (cm^{-1}): 1640 ($\nu_{C=C}$), 3340 (ν_{O-H}).

PMR ($CDCl_3$), δ(ppm): 0.74–1.52 (m, 7 H, 3 CH_2's & ), 1.06-1.14 (2 s, ), 1.72 (s, 3 H, ), 1.58-2.32 (m, 1H, ), 3.64-3.96 (m, 1H, C$\underline{H}$-OH), 4.62 (s, 2H =C$\underline{H}_2$).

Mass spectrum, m/e (rel. ab.): 166 (M^+).

Reaction of α,2-Diphenyl Cyclopropanemethanol (107) with Acetonitrile and Sulphuric Acid: Formation of N-(1,4-diphenyl-3-butenyl)acetamide (118a)

1.0 ml of acetonitrile was slowly added during 15 min. to 0.10 ml (2 mmol) of conc. H_2SO_4 at -20°C (ice-common salt bath). After 30 min. of stirring, a solution of the cyclopropanemethanol 107 (0.224 g, 1 mmol) in 1.0 ml acetonitrile was slowly introduced during 15 min. time. A red colour was formed during addition which instantly disappeared. After stirring for additional 40 min. at -20°C, the reaction mixture was poured into an ice cold solution of 10% $NaHCO_3$ (10 ml). Extraction of the reaction mixture with ethyl acetate (3 x 15 ml), washed with water (10 ml), brine (10 ml) and drying over anhyd. Na_2SO_4 followed by evaporation of the solvent under reduced pressure gave a crude solid, which was purified by thick layer chromatography (silica gel) using benzene-acetone, 85:15 as eluent to give the amide 118a. It was purified by recrystallization from chloroform-ether to obtain the pure amide, m.p. 116-117°C(d) (yield: 0.175 g, 66%).

IR (KBr), ν_{max} (cm^{-1}): 1610 ($\nu_{C=C}$), 1650 (ν_{C-NH}^{O}), 3325 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.92 (s, 3H, $-NH-\overset{O}{\overset{\|}{C}}-CH_3$), 2.6-2.78 (t, 2H, $=C-CH_2$, J = 7 Hz), 4.94-5.22 (q, 1H, $-CH-NHCOCH_3$), 5.68-6.48 (m, 2H, vinylic), 6.88-7.4 (m, 10 H, aryl).

Mass spectrum, m/e (rel. ab.): 265 (5, M^+), 222 (8, M^+-$COCH_3$), 207 (28, M^+-$NHCOCH_3$), 148 (53), 106 (100), 91 (13).

Anal. for $C_{18}H_{19}NO$, Calcd.: C, 81.51; H, 7.17; N, 5.28.
Found : C, 81.40; H, 6.98; N, 5.21%.

Reaction of the Cyclopropyl Carbinol (107) with Acrylonitrile and Sulphuric Acid: Formation of N-(1,4-diphenyl-3-butenyl)-propenamide (118b)

Following the same procedure, as described in the earlier reactions (again with 1 mmol of 107), but this time using acrylonitrile in place of acetonitrile, the reaction was carried out which gave after thick layer chromatographic separation (using benzene-acetone, 85:15 as eluent) and recrystallization from chloroform-petroleum ether (60-80°C), the amide 118b as a crystalline solid, m.p. 108°C (yield: 0.169 g, 61%).

IR (KBr), ν_{max} (cm^{-1}): 1610 ($\nu_{C=C}$ of PhC=C), 1630 ($\nu_{C=C-\overset{O}{\overset{\|}{C}}}$), 1655 ($\nu_{\overset{O}{\overset{\|}{C}-NH}}$), 3325 ($\nu_{N-H}$).

PMR ($CDCl_3$ + DMSO-D_6), δ (ppm): 2.66 (t, 2H, -C<u>H</u>$_2$-, J = 7 Hz), 4.84-5.2 (m, 1H, -CH-NH-), 5.48 (s, 1H, Ph-C<u>H</u>=), 5.76-6.48 (m, 4H, $=C\begin{matrix}\diagup \underline{H} \\ \diagdown CH_2\end{matrix}$ & CO-C<u>H</u>=C<u>H</u>$_2$), 6.8-7.54 (m, 10 H, aryl), 8.36 (d, 1H, N<u>H</u>, J = 8 Hz).

Mass spectrum, m/e (rel. ab.): 277 (7, M^+), 276 (28), 202 (30), 160 (88), 106 (100), 91 (13).

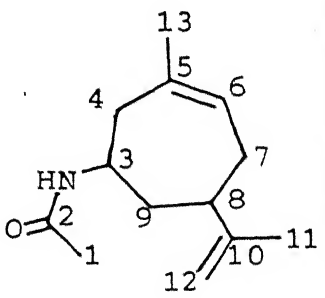
Anal. for $C_{19}H_{19}NO$, Calcd.: C, 82.31; H, 6.86; N, 5.05.
Found : C, 82.64; H, 6.88; N, 5.18%.

Reaction of the (108) with Acetonitrile and Sulphuric Acid: Formation of N-[3-methyl-6-(1-methylethenyl)cyclohept-3-enyl]acetamide (119a)

To 0.08 ml (1.5 mmol) of conc. H_2SO_4 at 0°C was slowly added 0.5 ml of acetonitrile. The mixture was stirred for about 30 min. and a solution of 0.166 g (1 mmol) of the cyclopropyl carbinol in 0.5 ml acetonitrile was slowly introduced during 15 mins. time. It was stirred for additional 20 mins. at 0°C and then poured into 5 ml of cold 10% sodium bicarbonate solution. Extraction with dichlororomethane washing with H_2O, brine, drying of the solvent with anhyd. Na_2SO_4 and evaporation of the solvent gave the crude amide 119a, which was purified by thick layer chromatography (silica gel) with benzene-acetone, 9:1 as eluent (yield: 0.072 g, 35%)(low melting solid).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1655 (br, $\nu_{C=C}$ & $-\overset{O}{\overset{\|}{C}}-NH$), 3430 ($\nu_{N-H}$).

PMR ($CDCl_3$), δ (ppm): 1.5 (s, 3H, H_3C / $NH-$), 1.73 (s, 3H, $H_2C=C(CH_3)$), 1.93 (s, 3H, $NHCOCH_3$), 1.2-2.43 (m, 7H, $-CH_2-$, allylic $-CH_2$'s & $-CH$), 2.53-2.87 (m, 1H, $-NH-CH-$), 4.7 (br,s, 2H, $>CH_2$), 5.27 (s, 1H, H_3C / H), 5.63 (br,s, 1H, $-NH-$).



^{13}C NMR ($CDCl_3$), δ(ppm): C_1, 21.6; C_2, 169.0; C_3, 45.9; C_4, 39.8; C_5, 147.6; C_6, 126.0; C_7, 37.2; C_8, 48.2; C_9, 32.5; C_{10}, 147.6; C_{11}, 27.6; C_{12}, 108.4; C_{13}, 32.2.

Mass spectrum, m/e (rel. ab.):.207 (33, M^+), 192 (19, M^+-CH_3), 179 (10), 166 (40), 165 (13), 164 (32), 112 (35), 100 (23), 99 (100), 70 (71).

Anal. for $C_{13}H_{21}NO$, Calcd.: C, 75.36; H, 10.14; N, 6.76.
Found : C, 75.59; H, 10.22; N, 6.82%.

Reaction of (108) with Acrylonitrile and Sulphuric Acid: Formation of N-[3-methyl-6-(1-methylethenyl)cyclohept-3-enyl]propenamide (119b)

The reaction was carried out exactly as the earlier reaction (on the same scale) using acrylonitrile in place of acetonitrile, and the reaction time being 20 min. at 0°C. Work-up and separation as before gave the amide 119b as a thick liquid (yield: 0.089 g, 41%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1600 & 1623 ($\nu_{C=C}$), 1660 (ν_{C-NH}^{O}), 3420 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.58 (s, 3H, H_3C with NH), 1.66 (s, 3H, $H_2C=C(CH_3)$), 1.12-2.50 (7H, $-CH_2-$, allylic $-CH_2$'s & $-CH$), 2.54-2.84 (m, 1H, $CH-NH-$), 4.64 (br,s, 2H, $=CH_2$), 5.40-5.66 (br,m, 3H, $=C(H)CO$, $=C(H)CH_2$ & $-NH$), 5.96-6.20 (2H, $H_2C=C(H)-CO$).

Mass spectrum, m/e (rel. ab.): 219 (46, M^+), 204 (10), 162 (21), 151 (24), 148 (20), 133 (16), 112 (53), 108 (61), 93 (65), 58 (100).

Anal. for $C_{14}H_{21}NO$, Calcd.: C, 76.71; H, 9.56; N, 6.39.
Found : C, 76.49; H, 9.32; N, 6.24%.

Preparation of 2-Phenylcyclopropanemethanol (109)

To a stirred slurry of 0.40 g (6.1 mg-atom) of Zn-Cu couple in 1.0 ml ether was added a solution of methylene iodide

as a thick gum (yield: 0.087 g, 58%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1675 (ν_{C-NH-}^{O}), 3420 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.96 (s, 3H, $NH-\overset{O}{\overset{\|}{C}}-CH_3$), 1.66-1.92 (m, 2H, $=C-CH_2-$), 2.54 (br,t, 1H, $-\overset{H}{N}-CH-$, J = 7 Hz), 4.84-5.78 (m, 3H, vinylic), 6.84-7.44 (m, 5H, aryl).

Mass spectrum, m/e (rel. ab.): 189 (22.3, M^+), 148 (64), 129 (14), 116 (57), 114 (22), 106 (100), 104 (31), 91 (20).

Anal. for $C_{12}H_{15}NO$, Calcd.: C, 76.19; H, 7.94; N, 7.41.
Found : C, 76.31; H, 8.05; N, 7.50%.

Reaction of 2-Phenyl cyclopropanemethanol (109) with Acrylonitrile and Sulphuric Acid: Formation of N-(1-phenyl but-3-enyl)-propenamide (122b)

The reaction was carried out in the same manner as above with acrylonitrile in place of acetonitrile for 2 hr. at 0°C. Purification as before gave the amide 122b as a thick gum (yield: 0.102 g, 64%).

IR ($CHCl_3$), ν_{max} (cm^{-1}): 1600 & 1625 ($\nu_{C=C}$), 1665 ($\nu_{C=O}$), 3420 (ν_{N-H}).

PMR ($CDCl_3$), δ (ppm): 1.68-2.14 (m, 2H, $=C-CH_2-$), 2.58 (t, 1H, $-NH-CH-$), J = 7 Hz), 4.9-6.2 (m, 6H, vinylic), 6.84-7.36 (m, 5H, aryl).

Mass spectrum, m/e (rel. ab.): 201 (20, M^+), 160 (55), 130 (15), 117 (51), 115 (26), 106 (100), 104 (31), 91 (28), 58 (18).

Anal. for $C_{13}H_{15}NO$, Calcd.: C, 77.61; H, 7.46; N, 6.97.
Found : C, 77.80; H, 7.61; N, 7.16%.

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CHAPTER II

DEVELOPMENT OF NOVEL REAGENTS FOR ORGANIC SYNTHESIS

A combination of two reagent systems viz., (1) Sodium iodide-boron trifluoride etherate ($NaI-BF_3.Et_2O$) and (2) Zinc-chlorotrimethylsilane ($Zn-ClSiMe_3$) have been developed and utilized in carrying out a number of interesting functional group transformations. These studies are presented in this chapter in two parts, A and B.

PART - A: TRANSFORMATIONS UTILIZING NaI-BF_3.Et_2O REAGENT SYSTEM

By using NaI-BF_3.Et_2O, four different kinds of synthetic transformations have been carried out and they are presented below:

II.A.1 Conversion of Allylic and Benzylic Alcohols into Corresponding Iodides

II.A.1(i) Background

Conversion of alcohols to iodides is an important reaction as alkyl iodides have widespread application in organic synthesis. Of the three alkyl halides, the carbon-halogen bond in alkyl iodides is the most polar and hence is most reactive towards nucleophilic substitution reactions. Thus, alkyl iodides have been frequently used as alkylating agents in organic reactions. Besides the C-C bond forming reactions, a large number of functional groups such as CN^-, NO_2^-, NH_2 etc. have been introduced in the place of iodide in an alkyl iodide. Furthermore, alkyl iodides are also useful in coupling reactions[1] and especially useful in preparing organometallic reagents like Grignard reagents, alkyl lithiums etc.

The classical methods for converting alcohols to iodides are (a) use of red phosphorus and molecular iodine[2] and (b) hydroiodic acid[3] (HI), which is usually generated *in situ* from alkali iodide with phosphoric acid-P_2O_5 or sulphuric acid. Although these reactions are useful for simple primary alcohols, complications with other alcohols (such as allylic and

tertiary) are reported.[4] Use of HI sometimes results in the reduction of alkyl iodide to alkane, and in case of allylic alcohol the double bond gets reduced and undesired products are obtained[3] (Scheme II.1):

$$(C_6H_5)_2CHI \quad \not\longleftarrow \quad (C_6H_5)_2CHOH + HI \longrightarrow (C_6H_5)_2CH_2$$

$$CH_3CH{=}CHCH_2I \quad \not\longleftarrow \quad CH_3CH{=}CHCH_2OH + HI \longrightarrow CH_3CHICH_2CH_3$$

SCHEME II.1

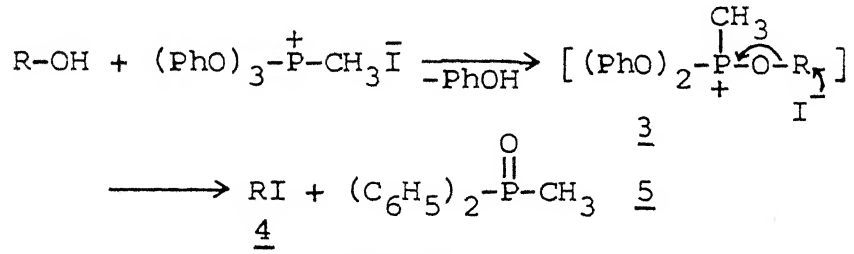
The quest for newer reagents, which are mild and selective has led to the discovery of several reagents based on phosphorus, boron and silicon derivatives. With these reagents the alcohol is activated by the strong P-O, B-O or Si-O bond (bond strengths in kJ/mol : C-O, 336; B-O, 560; P-O, 380; Si-O, 368) which provide a large part of the driving force for the nucleophilic attack by iodide ion, leading to formation of alkyl iodides.

Rydon et al.[5] were the first to demonstrate the utility of quasiphosphonium halides for halogenation of alcohols. These reagents viz., methyl triphenoxyphosphonium iodide (1) and iodophenoxyphosphonium iodide (2), were prepared as crystalline compounds through reaction of triphenylphosphite with methyl iodide and iodine, respectively.

$(C_6H_5)_3\overset{+}{P}\text{-}CH_3I^-$ (1) $\qquad$ $(C_6H_5O)_3\overset{+}{P}\text{-}I\ I^-$ (2)

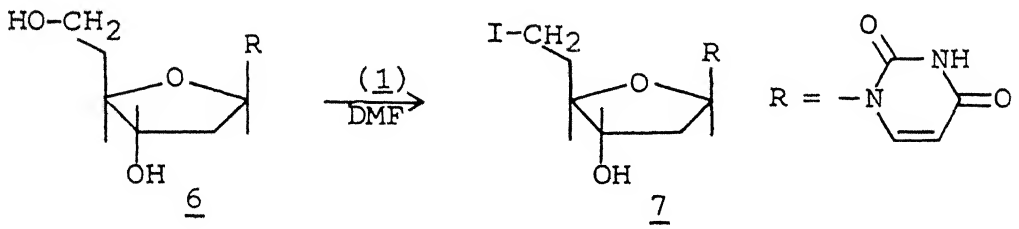
The reaction of alcohols with 1 proceeds via a nucleophilic attack of oxygen on phosphorus with the expulsion of phenol

and formation of an alkoxy phosphonium salt 3 , which then collapses to alkyl iodide 4 and diphenylmethyl phosphonate (5) (Scheme II.2):



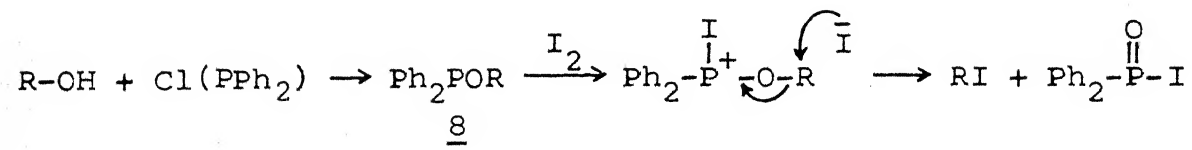
SCHEME II.2

It has been observed that although secondary -OH groups also react with 1 , it is possible to effect selective iodination of only the primary -OH function.[6] This is illustrated in the reaction of thymidine (6) with 1:1 equivalents of 1 in DMF which gives the 5'-deoxy-5'-iodothymidine 7 (Eqn. II.1).



..II.1

Chlorodiphenyl phosphine has been found to react with alcohols to form alkyl diphenylphosphinites 8 , which on reaction with iodine can be cleaved to give alkyl iodides,[7] (Scheme II.3):

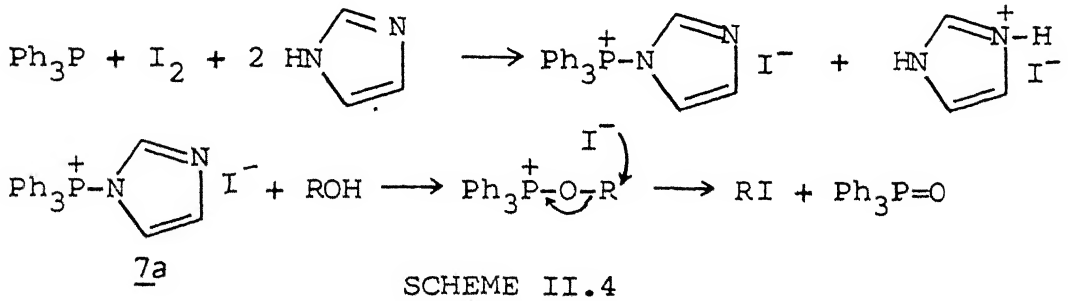


SCHEME II.3

A variety of alcohols such as primary, secondary, tertiary,

allylic and benzylic have been converted into iodides with this reagent.

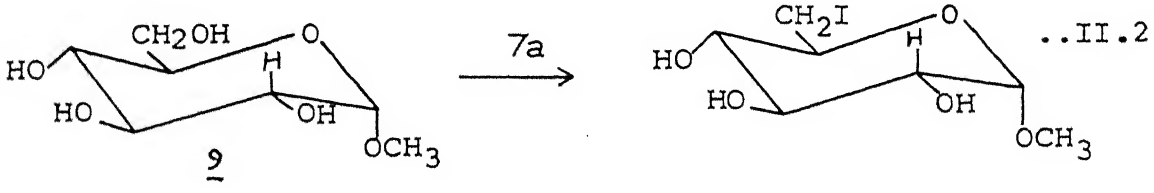
A combination of triphenylphosphine, imidazole, and iodine in toluene at reflux temperature furnishes a two phase system, which has recently been shown to be highly efficient in transforming alcohols to iodides[8] (Scheme II.4):



7a

SCHEME II.4

This reagent system exhibits steric selectivity and has been used in carbohydrate chemistry for selective conversion of primary alcohols to iodides, as shown in the case of methyl pyranoside 9 (Eqn. II.2). The secondary -OH groups remain untouched in the reaction.



..II.2

Several other phosphorus based reagent systems, such as, $(C_6H_5)_3P/I_2$;[9] $(C_6H_5)_3P/CCl_4/NaI$;[10] o-phenylene phosphochlorodite/I_2;[11] P_2I_4[12] etc., have been successfully used, for converting all types of alcohols to iodides.

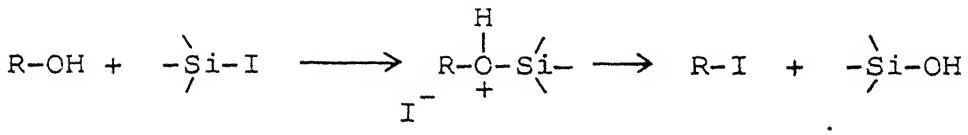
A simple method for the preparation of iodides, from both aliphatic and alicyclic alcohols, in high yields, by

activation with boron, has been reported by Fregguard and Long.[13] The method involves reaction of an appropriate alcohol with iodine in the presence of diborane (Eqn. II.3) or sodium borohydride (Eqn. II.4). This method is fairly inexpensive as low molar ratio of reagent:alcohol is required for the conversion.

$$6\ CH_3OH + 3\ I_2 + B_2H_6 \longrightarrow 6\ CH_3I + 2\ H_3BO_3 + 3\ H_2 \quad ..(II.3)$$

$$3\ CH_3OH + 2\ I_2 + NaBH_4 \longrightarrow 3\ CH_3I + H_3BO_3 + NaI + 2\ H_2 \quad ..(II.4)$$

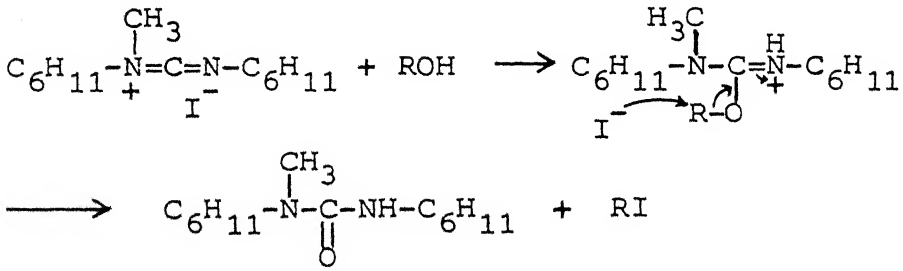
In recent years organosilicon reagents have become very popular, especially in C-O bond cleavage reactions. Iodotrimethylsilane, developed independently by Olah et al.[17] and Jung et al.,[18] has been shown to be a versatile reagent for converting all types of alcohols to their corresponding iodides in good yields. Because of its hydrolytic susceptibility and sensitivity in air, several convenient alternative methods for in situ generation of iodotrimethylsilane have been reported. These include use of phenyltrimethylsilane/iodine,[19] allyltrimethylsilane/iodine,[20] hexamethyldisilane/iodine[21] as well as chlorotrimethylsilane/sodium iodide,[14] in dry acetonitrile. A recent discovery from Olah's group[15] is the trichloromethylsilane/sodium iodide system which is an inexpensive alternative to iodotrimethylsilane. The mechanism of iodide formation, with these reagents, involves cleavage of the initially formed activated silylether by iodide ion (Scheme II.5).



SCHEME II.5

These reagents are extemely reactive and convert all types of alcohols viz., primary, secondary, tertiary, allylic and benzylic alcohols into corresponding iodides.

In addition to the phosphorus,boron and silicon based reagents, several other electrophilic reagents have been successfully utilized for activating alcohols. These include methanesulphonyl chloride,[22] p-toluenesulphonyl chloride,[23] and cyanuric chloride,[24] which along with sodium iodide convert all alcohols to iodides. Another useful reagent is dicyclohexylcarbodiimide methiodide,[25] whose reaction with alcohols is shown in Scheme II.6:

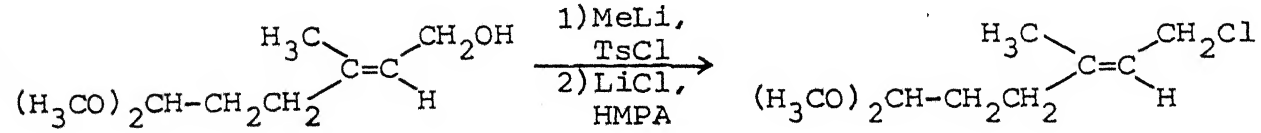


SCHEME II.6

Once again this reagent is reactive towards all type of alcohols.

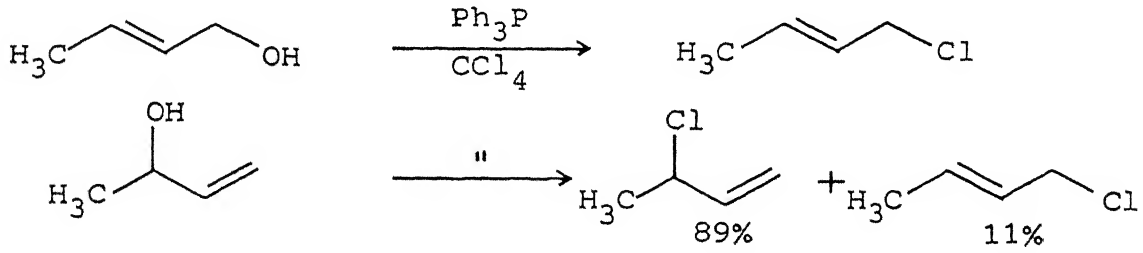
Selective Conversion of Allylic and Benzylic Alcohols into Halides

Unlike saturated alcohols, the sensitive nature of the allylic system, in allylic alcohols, poses regio- and stereochemical problems during halide preparation. For a method to be synthetically useful, it should have the following features: (a) the reaction should be regiospecific leading exclusively to either α- or γ-substituted product in a predictable manner, (b) the stereochemistry at the β,γ-double bond should be preserved, and (c) the reaction conditions, work-up and isolation must be mild enough that neither allylic rearrangement nor solvolytic elimination of the product occurs. Several reagent systems have been reported, which more or less satisfy these conditions. Young et al.[26] found that $SOCl_2$ in ether gives exclusively the rearranged products; in the presence of a tertiary amine, however, the regioselectivity is changed in favour of the unrearranged α-attack product.[27] Phosphorus halides have also been reported to give unrearranged products with primary allylic alcohols under varying sets of conditions.[28] Stork et al.[29] have employed chloride ion substitution of a tosylate prepared *in situ*, leading to regiospecific α-attack (Eqn. II.5)



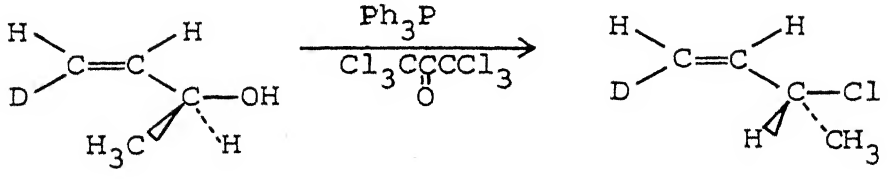
..(II.5)

The reagent system triphenylphosphine-carbon tetrachloride(or carbon tetrabromide)[30] has been found to be useful for conversion of allylic alcohols to halides. While primary allylic alcohols give unrearranged halides, the reaction with secondary allylic alcohols leads to some rearranged halides (Scheme II.7):



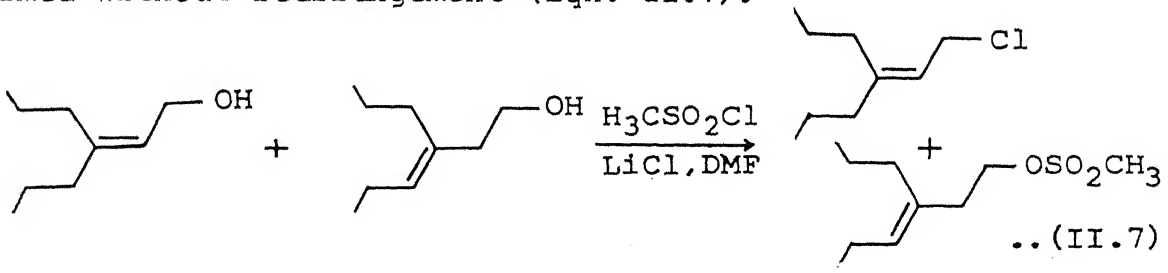
SCHEME II.7

The principal drawback of the Ph_3P-CCl_4 method is that lower molecular weight allylic chlorides have boiling point very close to that of CCl_4, thereby causing difficulties in isolation. To avoid these problems, Magid et al.[31] replaced CCl_4 by hexachloroacetone, a higher boiling source of positive halogen. This modified procedure gives high regioselectivity with primary and secondary alcohols and the double bond geometry is quantitatively preserved, and inversion of configuration occurs at α-carbon (Eqn. II.6).



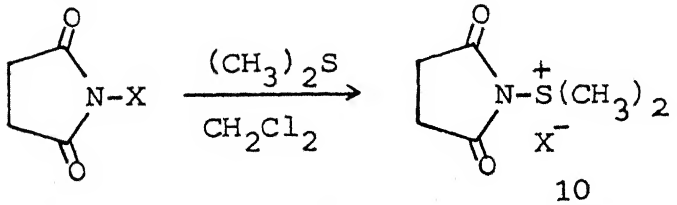
..(II.6)

All the reagents discussed above, although are suitable for preparation of allylic halides, they do not exhibit any special chemoselectivity towards allylic alcohols alone. Although allylic and benzylic alcohols are definitely more reactive, other alcohols also form halides albeit kinetically at a lower rate with these reagents. The reagent system methanesulphonyl chloride-LiCl-DMF, has been shown by Collington and Meyers[32] to be specific for the conversion of allylic alcohols to chlorides. Any non-allylic alcohol, present along with the allylic alcohol, was converted to the mesylate and not the chloride. Also the allylic halide was formed without rearrangement (Eqn. II.7):



..(II.7)

The only reagent available in the literature, which is highly selective and is capable of distinguishing allylic and benzylic alcohols and interacting with these, leaving the non-allylic and benzylic alchols totally untouched, is that discovered by Corey et al.[33] N-Chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) form a 1:1 complex 10 with dimethylsulphide (Eqn. II.8) which converts allylic and benzylic alcohols

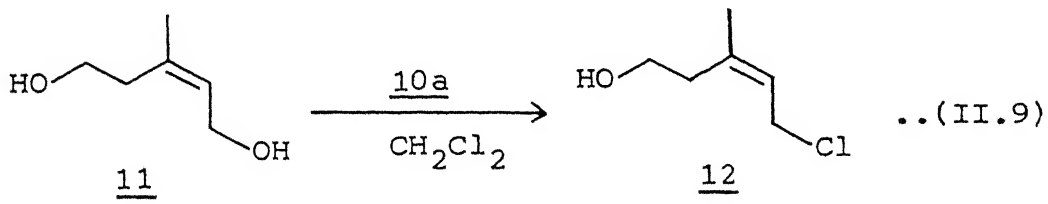


a, X = Cl
b, X = Br

..(II.8)

10

stereospecifically into the corresponding halide. A mixture of cyclohex-2-en-1-ol and cyclohexanol with either of the reagent gave exclusively, the cyclohexenyl halide with complete recovery of cyclohexanol. In an impressive experiment, Corey et al. have reacted Z-3-methyl-2-penten-1,5-diol 11 with the NCS-DMS complex 10a and obtained the allylic monochloride 12 , in which the other -OH group was untouched (Eqn. II.9). Similarly benzylic alcohol can be made to react



11 12 ..(II.9)

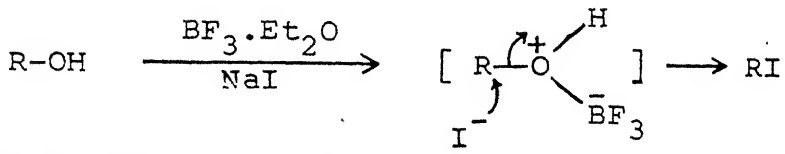
in the presence of a non-benzylic alcohol to give the benzylic halide exclusively. Such reagents which are sufficiently selective to distinguish functional groups of the same class are exceedingly valuable in synthesis involving multifunctional molecules, since they permit operations which are either impossible or depend upon the use of protective groups.

II.A.1(ii) Present Work

It is apparent from the background part of this section, that although there are a number of reagents available for the conversion of all types of alcohols, viz., primary, secondary, tertiary, allylic and benzylic alcohols, into the corresponding iodides, there is no reagent reported which reacts with only the allylic and benzylic alcohols. Such is not the case with chlorides and bromides since a complex of dimethyl sulphide with either N-chlorosuccinimide or N-bromosuccinimide has been reported to selectively convert allylic and benzylic alcohols into chlorides or bromides respectively.[33] In view of this, and the fact that iodides are more reactive than the corresponding chlorides or bromides, we undertook a study to develop a reagent system for such a conversion. In the present study, we have successfully developed a reagent system consisting of sodium iodide (NaI) and boron trifluoride etherate ($BF_3.Et_2O$), which selectively converts only allylic and benzylic alcohols into the corresponding iodides.

The utility of $BF_3.Et_2O$ as a versatile reagent in organic chemistry is well documented.[34] An easy release of the BF_3 component (a Lewis acid) from this complex and its further coordination with either oxygen atom or other heteroatoms of the substrates, and thereby bringing about specific transformations has also been well exploited in organic reactions.[34b]

Using the combination of $BF_3.Et_2O$ and NaI a number of allylic and benzylic alcohols (Table II.1) were converted to the corresponding iodides in good to excellent yields under very mild conditions. A simple probable mechanism for this reaction is illustrated in Scheme II.8.



(R = allyl or benzyl group)

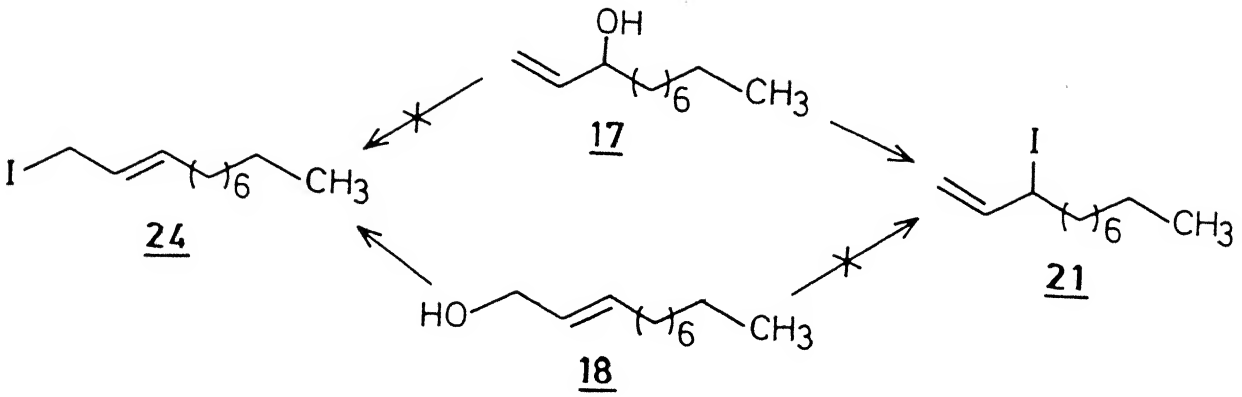
SCHEME II.8

Thus, coordination of the hard acid i.e., BF_3 with the hard basic oxygen of alcohol followed by the attack of the soft basic iodide ion on a carbon which is also a soft acid by virtue of its being either allylic or benzylic, leads to the formation of the iodide.

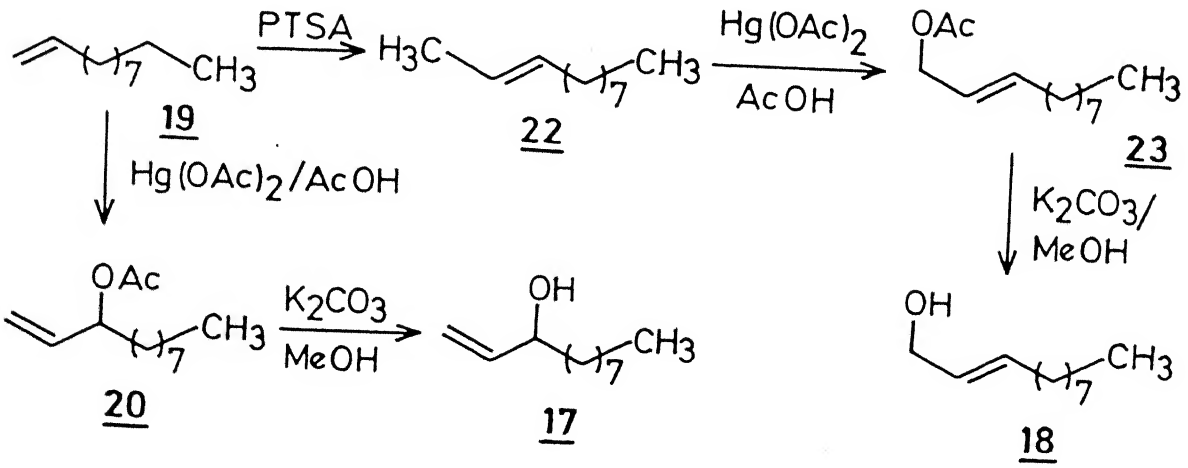
In every case the reaction was conducted using the molar ratio of alcohol: $BF_3.Et_2O$:NaI as 1:2:2. Thus, when cinnamyl alcohol (13) was reacted with this reagent system in acetonitrile, first at 0°C for 15 minutes followed by 15 minutes reaction at room temperature, cinnamyl iodide (14) was obtained in 74% yield without any trace of the rearranged iodide. The structure of this iodide was further confirmed by its spectral characteristics (Sec. II.A.1(iii)). In a similar fashion geraniol (15) was converted into its corresponding iodide 16 (in 70% yield in 25 mins. at 0°C). The spectral characteristics of the product 16 obtained by us were similar to the one reported in literature,[35] by other

workers. From this example, two salient features are apparent: (i) no allylic rearrangement takes place, and (ii) an isolated olefin is unaffected under these conditions.

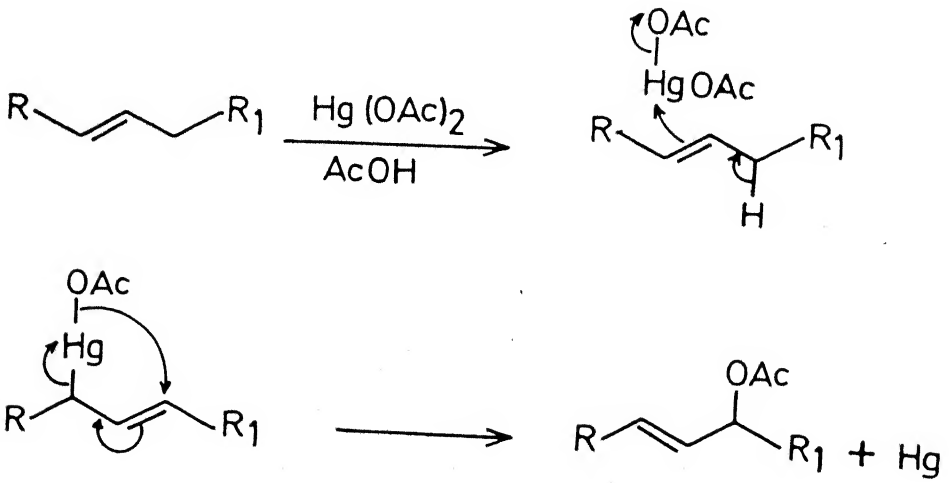
1-Undecene-3-ol (17) and (E)-2-undecene-1-ol (18) are representative examples of two typical alcohols in which the alcoholic group is interchanged. These substrates were so chosen, that had there been an allylic rearrangement occurring, one alcohol would give the iodide corresponding to the other alcohol and vice-versa (Scheme II.9). Alcohols 17 and 18 were prepared as shown in Scheme II.10. A mechanism for acetoxymercuration is shown in Scheme II.11. Thus, 1-undecene (19) was reacted with $Hg(OAc)_2$ in acetic acid to give 3-acetoxyundecane (20) in 85% yield. The IR spectrum showed strong absorptions at 1650 cm^{-1} ($\nu_{C=O}$) and 1750 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$). Hydrolysis of this acetate with K_2CO_3 in methanol led to the formation of the alcohol 17 in 80% yield, b.p. 100°C (oil bath temperature) at 5.5 mm (lit.[36] b.p. 112-114°C/ 10 mm). In the IR spectrum of this alcohol an absorption at 3400 cm^{-1} (br, ν_{O-H}) was observed . The ^1H NMR spectrum showed absorptions at δ 3.9-4.1 (m, 1H, -C<u>H</u>-OH), 4.9-5.84 (m, 3H, olefinic). Its reaction with $NaI-BF_3.Et_2O$ for 45 mins. at 0°C, gave the allylic iodide 21 in 90% yield. The IR spectrum of this iodide showed a weak absorption at 1650 cm^{-1} ($\nu_{C=C}$) and absence of any -OH group which is characteristic around 3400 cm^{-1}. The ^1H NMR showed absorptions at δ 0.9 (t, 3H, -C<u>H</u>$_3$), 1.16-2.2 (m, 14H, -(C<u>H</u>$_2$)$_7$-), 3.72-4.0 (m, 1H, -C<u>H</u>-I) and 4.86-5.84 (m, 3H, olefinic). By comparison with ^1H NMR spectrum of the starting alcohol 17



SCHEME II·9



SCHEME II·10



SCHEME II·11

(cf. Figs. II.1 and II.2), it was found that the olefinic protons (d & e) and (c) the allylic -C-H α- to the iodide were similar in pattern, except that these protons were slightly shielded in the case of the iodide. This is expected as oxygen is more electronegative than iodine.

For the preparation of alcohol 18, 1-undecene was isomerized by using p-toluenesulphonic acid (PTSA) in refluxing benzene to obtain the (E)-2-undecene 22 in 78% yields, b.p.76°C/10 mm (lit.[37] b.p. 195°C). This olefin (22) was then regeoselectively acetoxylated with $Hg(OAc)_2$-HOAc to 1-acetoxy-(E)-2-undecene (23) in 70% yield. Its IR spectrum of 23 showed absorptions at 1645 cm^{-1} ($\nu_{C=C}$) and 1750 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$). The allylic acetate 23 was converted subsequently into the corresponding alcohol 18 by hydrolysis with K_2CO_3-CH_3OH at room temperature for 25 hrs. in 80% yield. The IR spectrum of this alcohol 18 showed absorptions at 1650 cm^{-1} ($\nu_{C=C}$) and 3400 cm^{-1} (ν_{OH}) and its ^1H NMR spectrum indicated absorptions at δ1.16-2.2 (m, 13H, O-H and $-(CH_2)_6-$), 3.24-3.6 (m, 2H, C=C-CH_2-), 3.84-4.14 (m, 2H, -CH_2-O-) and 4.90-6.0 (m, 2H, olefinic).

This alcohol 18 when reacted with NaI-$BF_3.Et_2O$, for 45 mins. at 0°C in acetonitrile gave the corresponding iodide (E)-undec-2-enyl iodide (24) in 95% yield. Its IR absorptions at 1655 cm^{-1} ($\nu_{C=C}$) and ^1H NMR absorptions at δ 0.88 (t, 3H, -CH_3), 1.22-2.22 (m, 12H, $-(CH_2)_6-$), 3.36 (t, 2H, J = 6 Hz, C=C-CH_2-), 3.74-3.86 (m, 2H, -CH_2-I), 4.92-5.78 (m, 2H, olefinic), were consistent with structure 24, i.e., the unrearranged iodide.

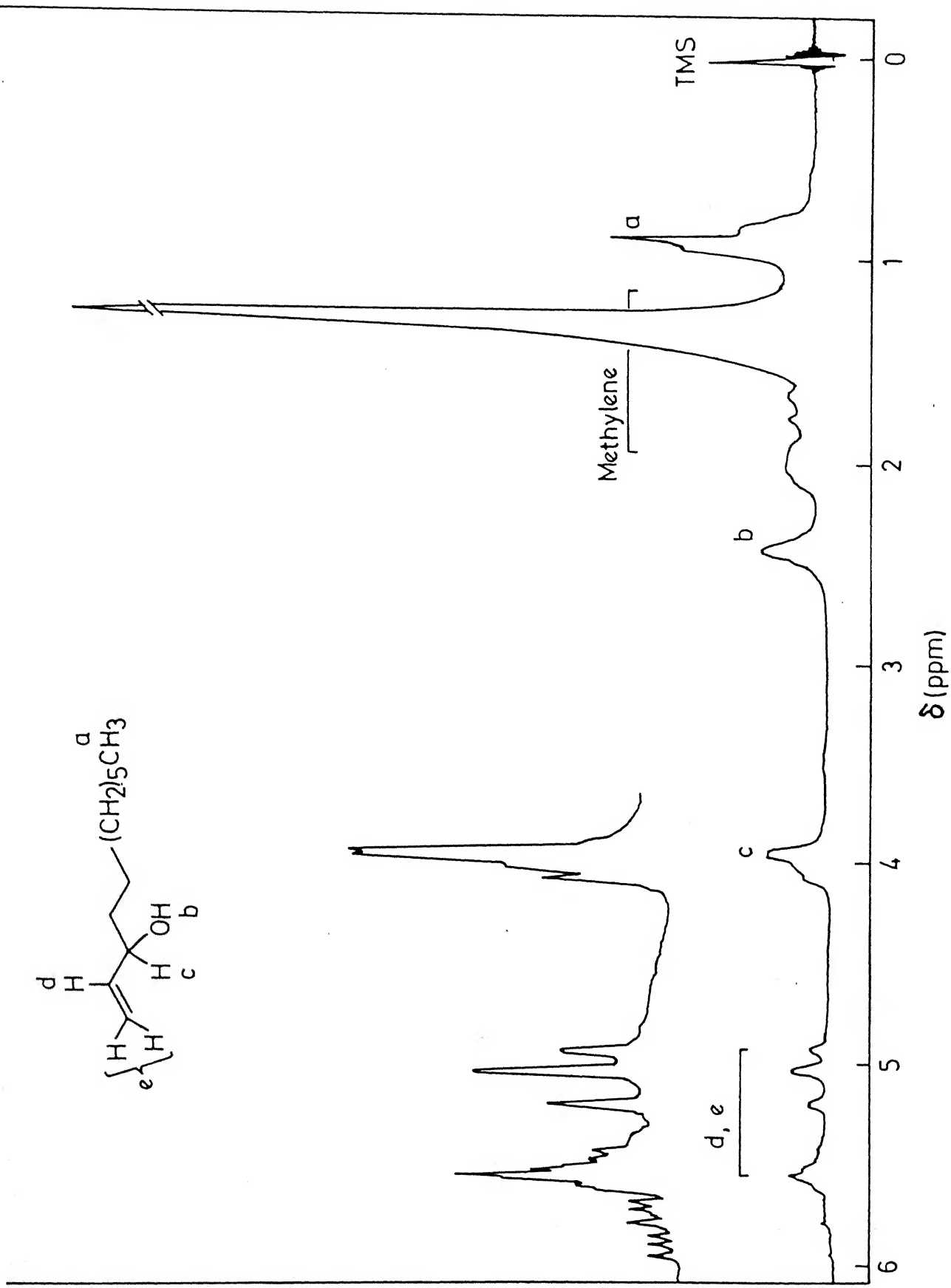
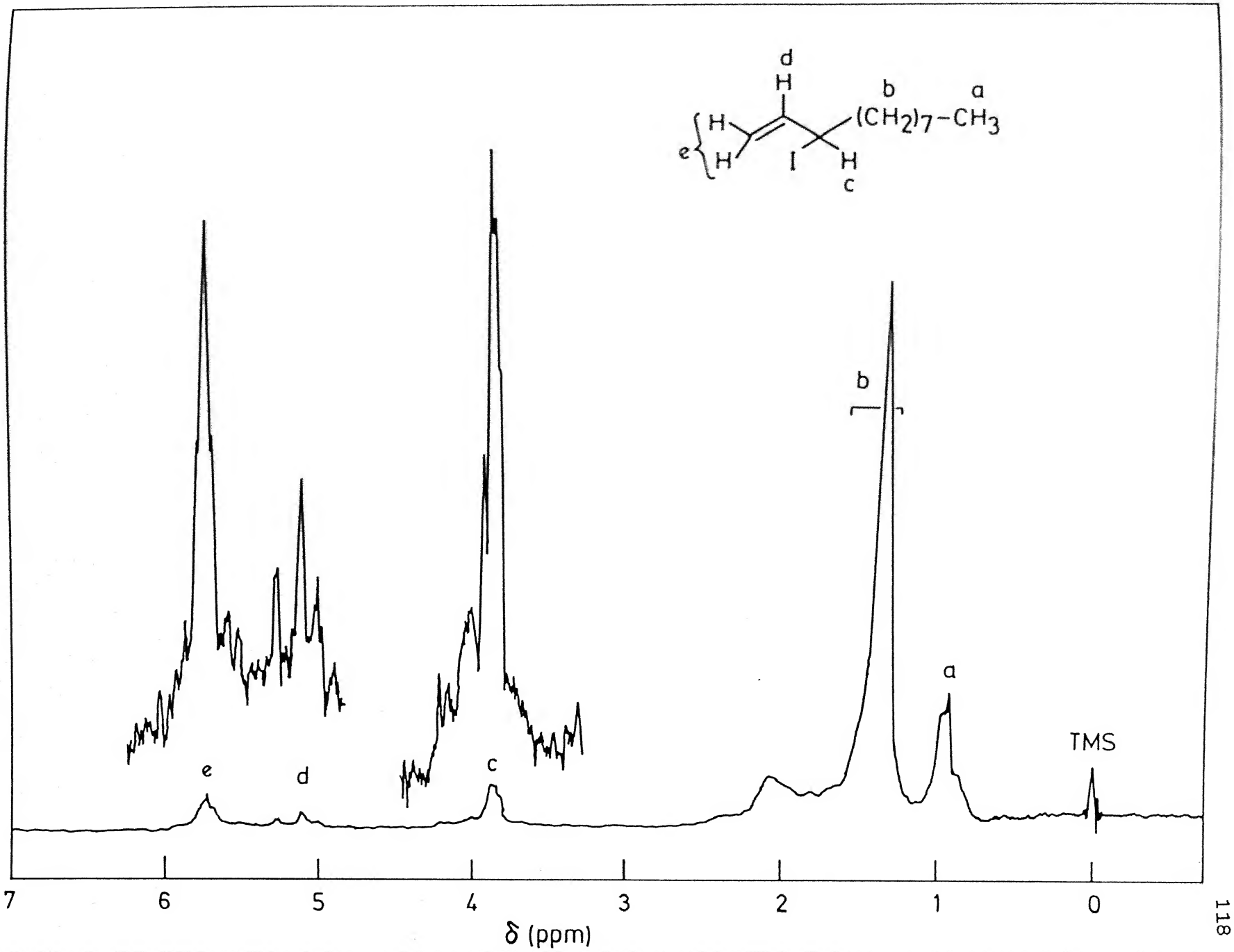
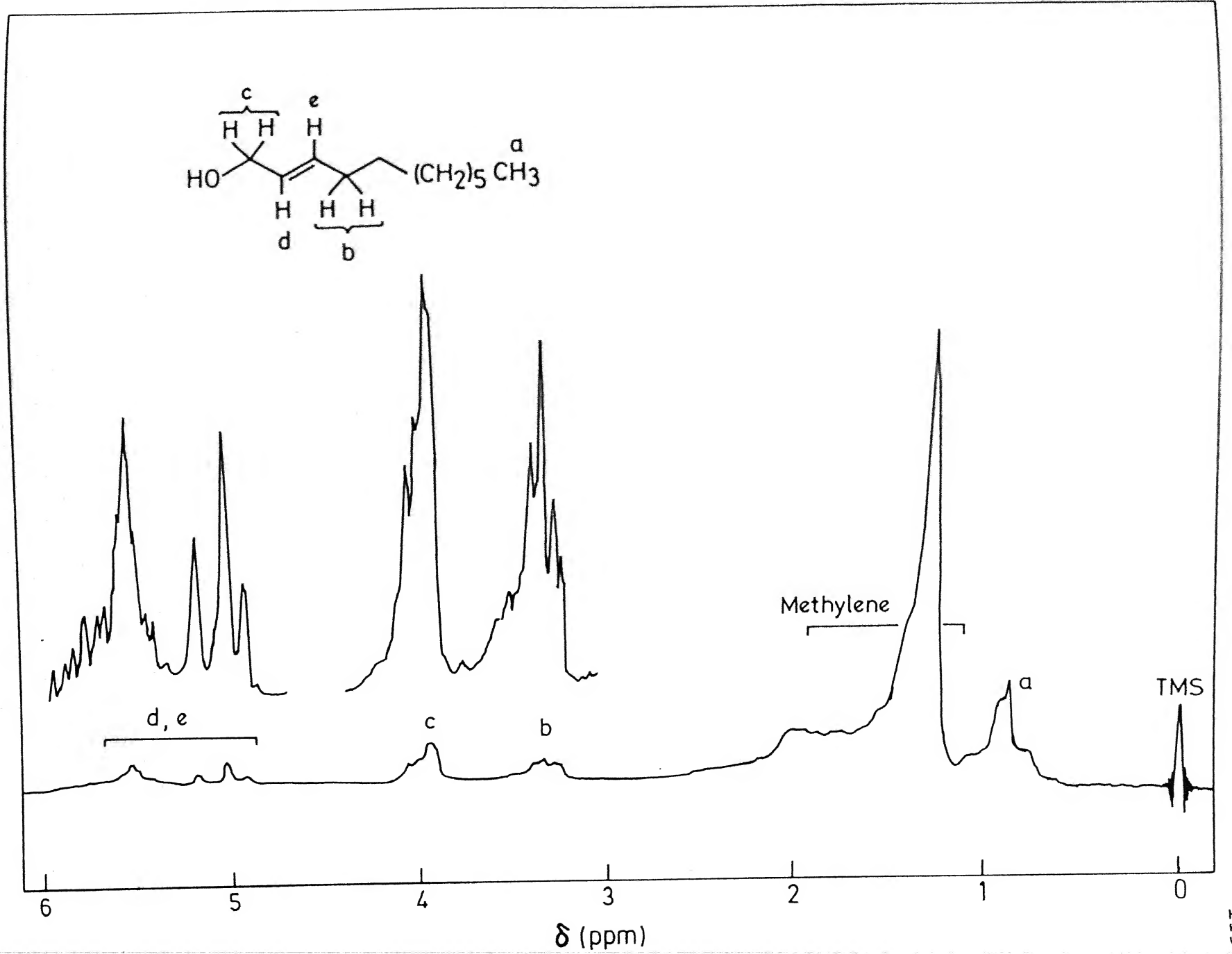
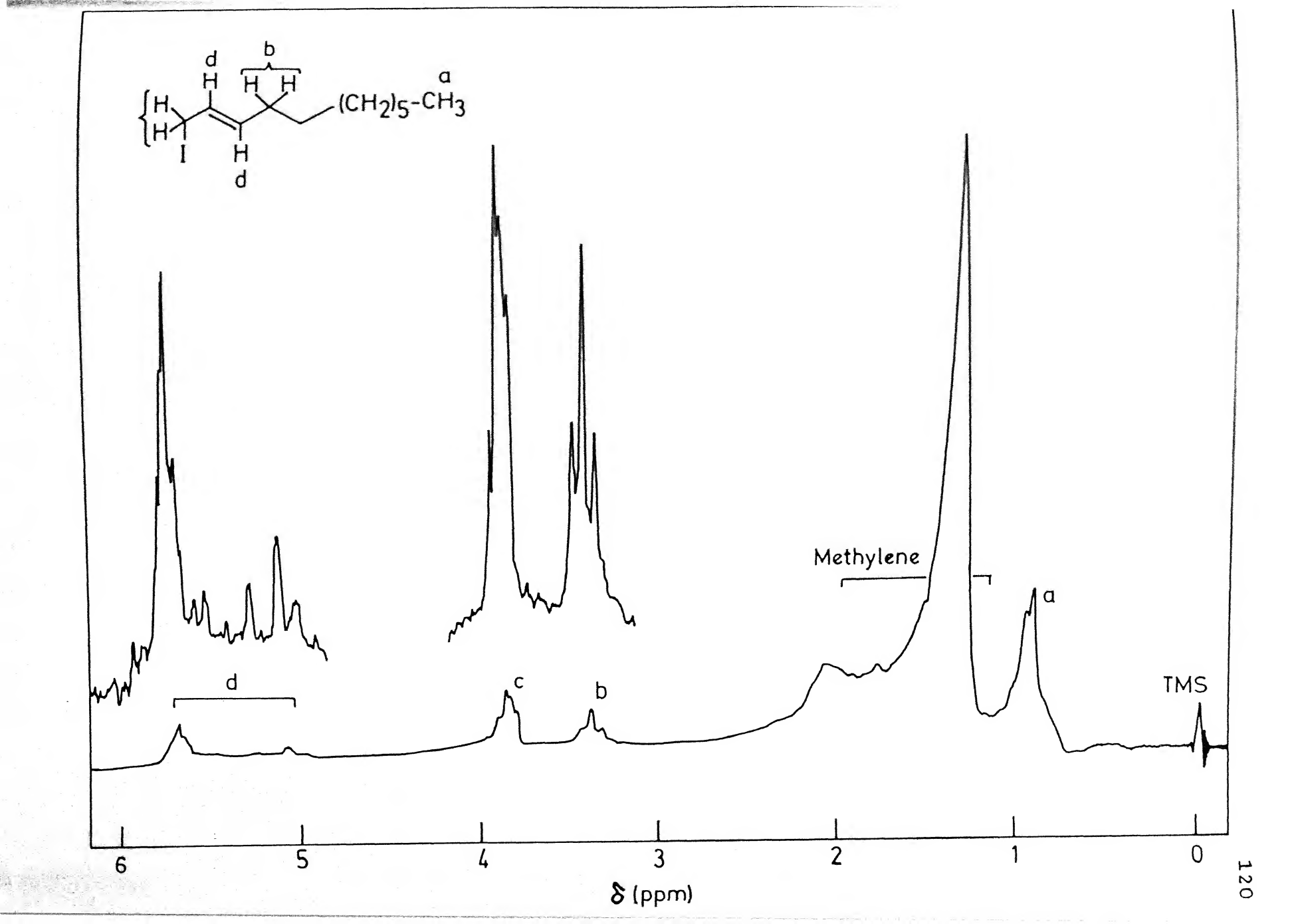


Fig. II·1 PMR Spectrum (100 MHz) of 17.

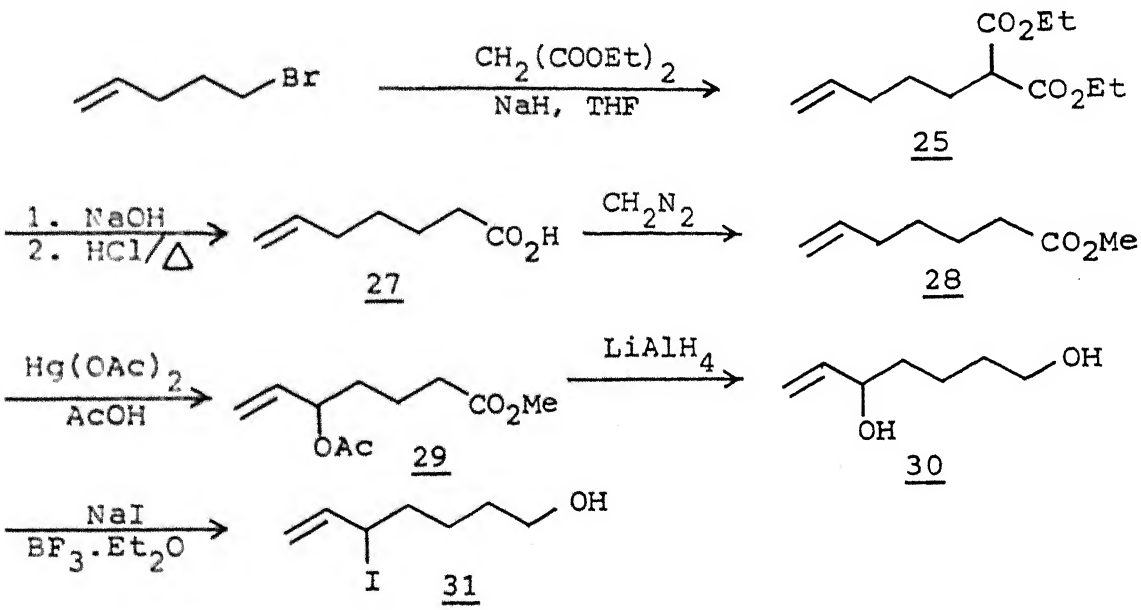

d
H
b
a
H
(CH2)7-CH3
e
H
I
H
c
b
a
TMS
e
d
c
7
6
5
4
3
2
1
0
δ (ppm)


c
e
H H
H
a
HO
(CH2)5 CH3
H
H H
d
b
Methylene
a
TMS
d, e
c
b
6
5
4
3
2
1
0
δ (ppm)


d
b
a
H
H
H
H
H
I
H
d
(CH2)5-CH3
Methylene
a
TMS
d
c
b
6
5
4
3
2
1
0
δ (ppm)

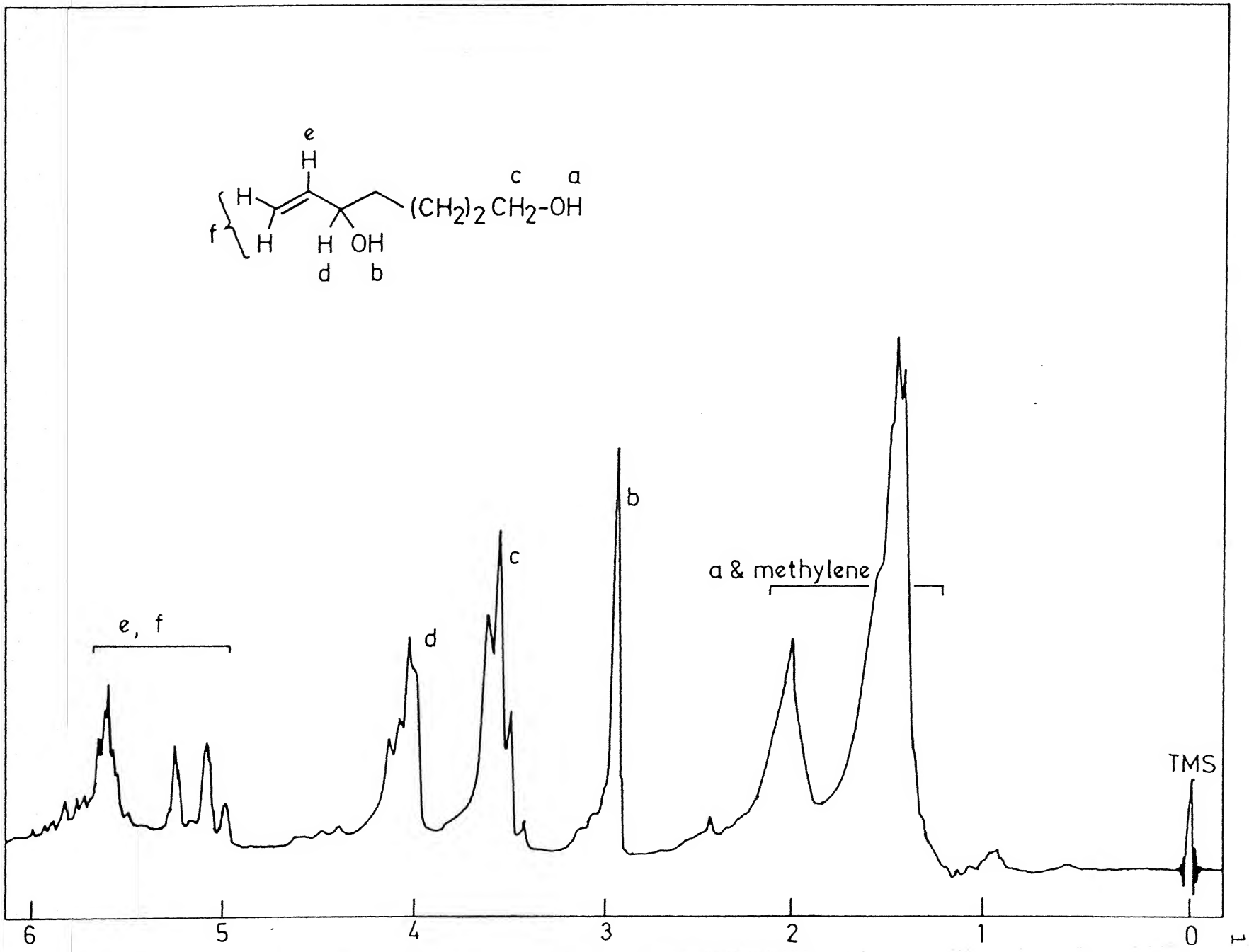
The mass spectrum showed M^+ ion peak at 280.

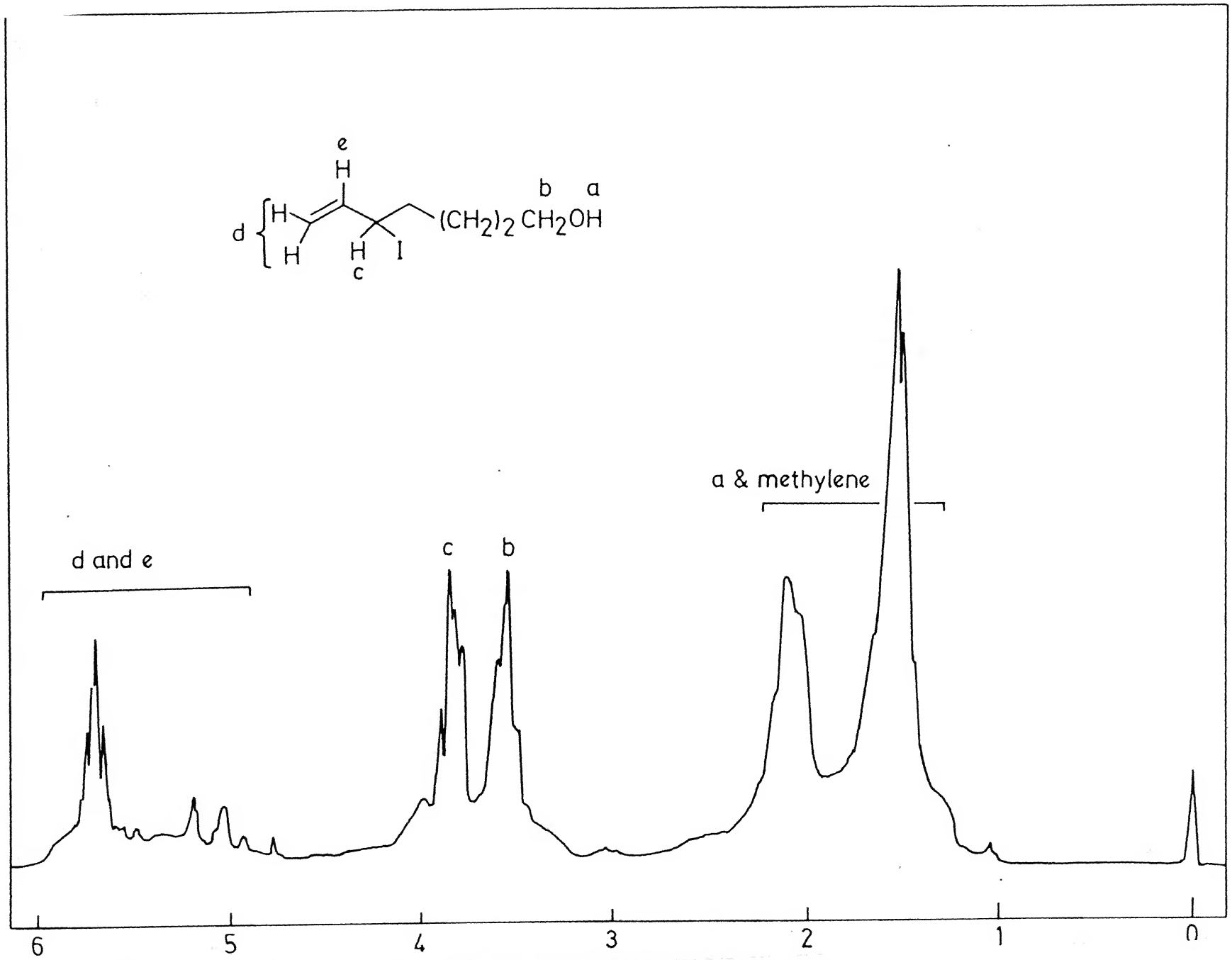
The above examples clearly indicated the generality of the reaction in case of allylic alcohols. We, therefore, chose to test the reactivity of an allylic alcohol in the presence of a saturated alcohol. For this purpose, a diol i.e., 2,6-dihydroxy-1-heptene 30 was prepared as illustrated in Scheme II.12.



SCHEME II.12

1-Pentenyl bromide was reacted with diethylmalonate in the presence of sodium hydride in refluxing THF for 7 hrs. to obtain diester 25 in 89% yield. Hydrolysis with aqeous potassium hydroxide for 12 hrs. at room temperature gave the dicarboxylic acid 26 in 90% yield, m.p. 56°C (lit.[38] m.p.57°C) whose decarboxylation with conc. HCl at 100°C for 17 hrs. gave the monocarboxylic acid 27 in 75% yield, b.p. 115-120°C/10 mm (lit.[38]


e
H
H
f
H
H
OH
d
b
c
a
(CH2)2 CH2-OH
e, f
d
c
b
a & methylene
TMS
6
5
4
3
2
1
0


e
H
b a
d
H
H
H
c
I
(CH2)2 CH2OH
a & methylene
d and e
c
b
6
5
4
3
2
1
0
τ

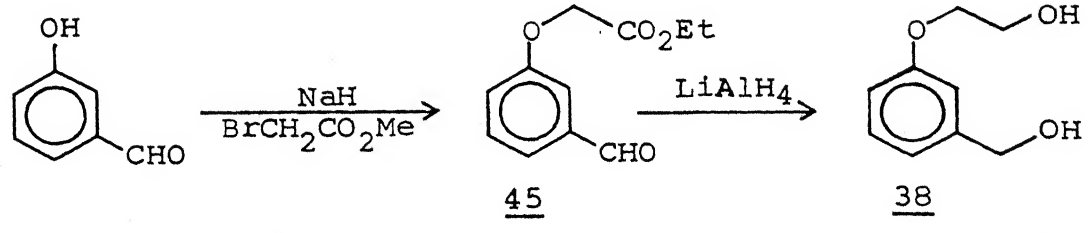
b.p. 125°C/15 mm). The corresponding methyl ester 28 was then obtained upon treatment with diazomethane in 95% yield, b.p. 8! 1 mm (lit.[39] b.p. 106.5°C/4 mm). Acetoxymercuration of this ester under similar conditions as described previously led to the formation of 5-acetoxy-Δ^6-methylheptenoate (29) in 81% yield whose IR spectrum showed strong absorptions at 1750 cm^{-1} ($\nu_{\overset{O}{\overset{\|}{C}}-OC}$ and $\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and 1655 cm^{-1} ($\nu_{C=C}$). Its ^1H NMR showed absorptions at δ 1.84 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$), 3.46 (s, 3H, $-C-\overset{O}{\overset{\|}{C}}O\underline{CH}_3$) and 4.86-5.84 (m, 3H, olefinic). Its lithium aluminium hydride reduction led to the formation of the required diol 30 in 89% yiel b.p. 100°C/0.1 mm (lit.[40] b.p. 105-107°C/0.6 mm). Its IR spect showed absorptions at 3350 cm^{-1} (br, ν_{OH}) and 1650 cm^{-1} ($\nu_{C=C}$), and its ^1H NMR indicated absorptions at δ 3.6 (t, 2H, $-C\underline{H}_2-O$, J = 6 Hz), 3.84-4.22 (m, 1H, C=C-C<u>H</u>-O), 4.98-6.6 (m, 3H, olefinic). The diol 30, when reacted with $NaI-BF_3.Et_2O$ at 0°C for 30 mins. resulted in the formation of the monoiodide 31 whose structure was confirmed by spectral data. Thus, in its IR spectrum absorption at 3400 cm^{-1} (br) was observed corresponding to ν_{O-H} and its ^1H NMR spectrum showed absorptions at δ 1.3-2.4 (m, 6H, $-(C\underline{H}_2)_3-$), 3.4 (t, 2H, $-OC\underline{H}_2-$, J = 6 Hz), 3.7 - 4.0 (m, 1H, I-C<u>H</u>-C=C-), 4.88-5.90 (m, 3H, olefinic).

These examples (vide supra) demonstrated the utility of $NaI-BF_3.Et_2O$ in regioselective conversion of allylic alcohols into the corresponding iodides, without allylic rearrangement.

Next, our attention was directed towards reaction with benzylic alcohols, and a set of substrates chosen (32-37) for

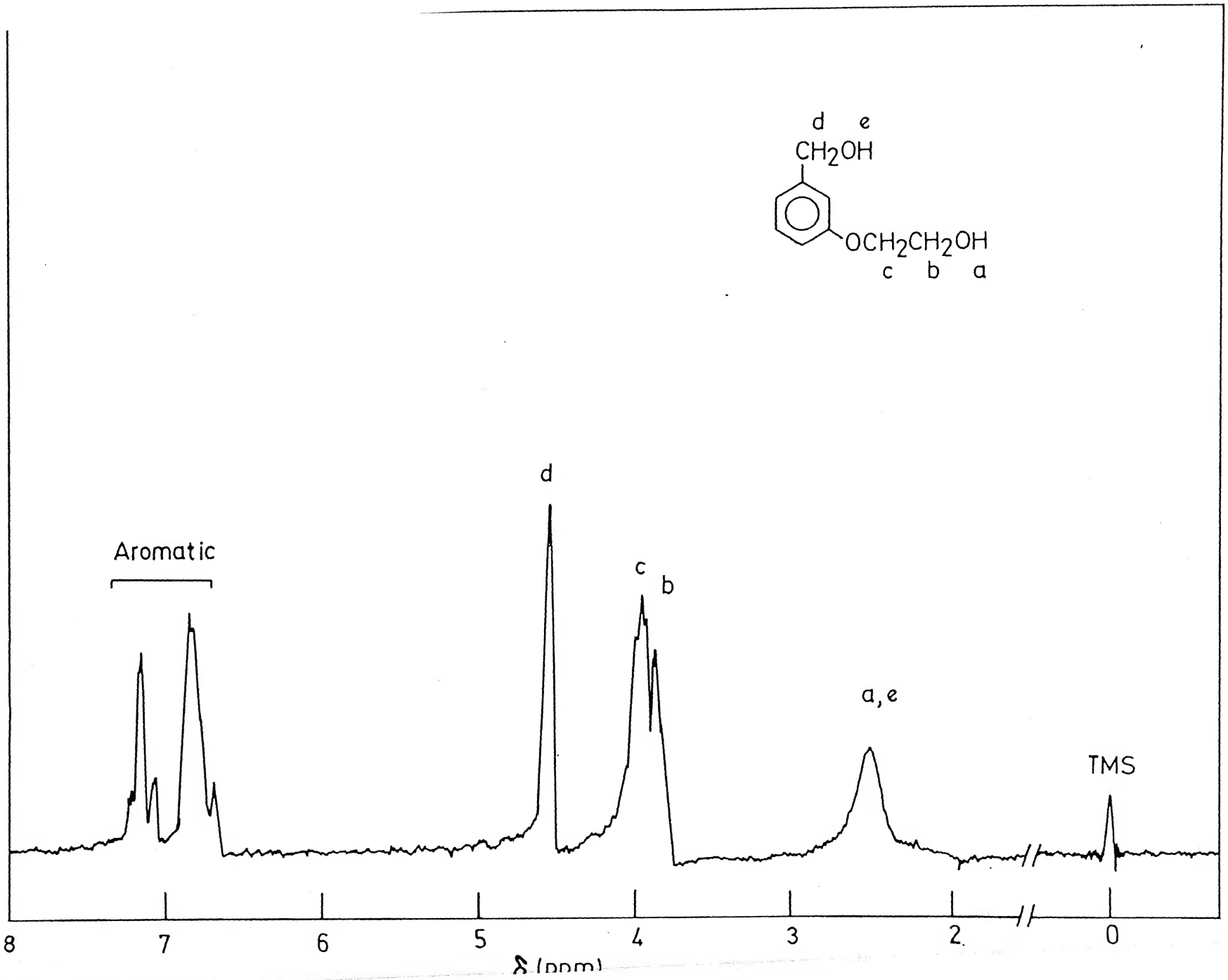
this study are listed in the Table II.1. The reaction of benz alcohol 37 with NaI-BF_3.Et_2O (2:2 molar equiv.) for 25 mins. i acetonitrile at room temperature gave 94% of benzyl iodide (39) b.p. 94°C/10 mm (lit.[41] b.p. 93°C/10 mm). Under similar conditions m-chlorobenzyl alcohol (34), p-chlorobenzyl alcohol (33), m-methoxybenzyl alcohol (35), 2-phenylethanol (36) and o-thiomethyl benzyl alcohol (37) were all converted smoothly to their corresponding iodides (40-44) in yields 92%, 91%, 92%, 93% and 98%, respectively. Their boiling points and melting points were comparable with those reported in the literature (cf. Table II. Spectral data of all these iodides were in complete agreement wi the structures assigned to them.

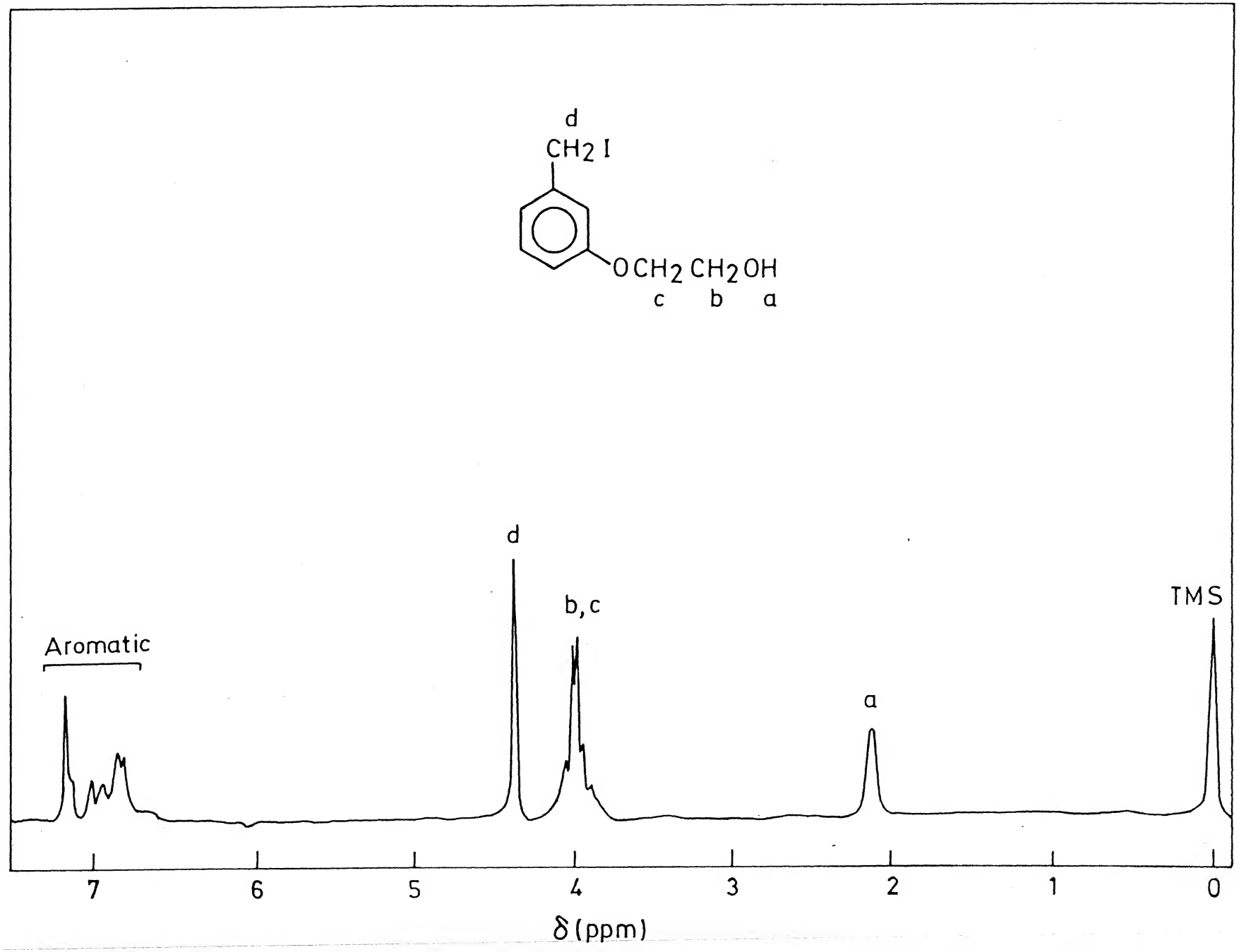
Once again a typical diol, i.e., 2-[(m-hydroxymethyl)phenoxy]ethanol 38 was chosen to demonstrate the chemoselective reaction of the benzylic alcohol in preference to non-benzylic saturated primary alcohol under the reaction conditions. The diol (38) was prepared as illustrated in Scheme II.13. m-Hydroxybenzaldehyde was condensed with methyl bromoacetate in the presence of sodium hydride to obtain the aldehydoester 45 in 82% yield (b.p. 120°C (oil bath temp., at 0.5 mm). IR (thin film) showed absorptions at 1720 cm^{-1} ($\nu_{C=O}^{H}$) and 1770 ($\nu_{C-OCH_3}^{O}$) and



45 38

SCHEME II.13


d e
CH2OH
OCH2CH2OH
c b a
Aromatic
d
c
b
a, e
TMS
8
7
6
5
4
3
2
0
δ (ppm)


d
CH2 I
OCH2 CH2 OH
c b a
d
b,c
TMS
Aromatic
a
7
6
5
4
3
2
1
0
δ (ppm)

^{1}H NMR absorptions at δ 3.8 (s, 3H, $-\overset{O}{\overset{\|}{C}}-OCH_3$), 4.7 (s, 2H, $-O-CH_2-$ $\overset{O}{\overset{\|}{C}}$), 7.04-7.72 (m, 4H, aryl) and 9.78 (s, 1H, $-\overset{O}{\overset{\|}{C}}-H$) were observed. Lithium aluminium hydride reduction of this compound gave the required diol 38, whose IR (KBr) spectrum showed absorption at 3350 cm^{-1} (br, ν_{O-H}) and its ^{1}H NMR showed absorptions at δ 2.5 (br, s, 2H, 2 -OH), 3.78-4.3 (m, 4H, $-O(CH_2)_2-$), 4.6 (s, 2H, $Ar-CH_2$) and 6.6-7.3 (m, 4H, aromatic). The mass spectrum showed M^+ peak at 168.

Reaction of this diol 38 with NaI-BF_3.Et_2O (2:2 molar equiv at 0°C for 30 mins. gave the iodide 46 in 91% yield, m.p. 74°C, whose IR (KBr) spectrum showed absorption band at 3350 cm^{-1} (br, ν_{O-H}) and ^{1}H NMR showed absorptions at δ 2.35 (s, 1H, -OH), 3.83-4.2 (m, 4H, $-O(CH_2)_2-OH$), 4.43 (s, 2H, $Ar-CH_2I$) and 6.77-7.27 (m, 4H, aromatic). The mass spectrum showed M^+ peak at 278. These data are in agreement with the structure assigned to this iodide 46.

The above study, for the facile conversion of allylic and benzylic alcohols into the corresponding iodides under extremely mild conditions clearly demonstrates the versatility of the NaI-BF_3.Et_2O combination. It is noteworthy, from the example 30 and 38 that non-allylic or non-benzylic primary alcohols are inert under the conditions of the reaction, whereas the allylic and benzylic alcohols in the same molecule are converted to the corresponding iodides. This kind of selectivity where functional groups of the same class are distinguished could be highly useful in organic synthesis, because this will obviate the necessity of

protecting the primary saturated alcohol (non-allylic or non-benzylic). In yet another experiment, cyclohexanol was treated with NaI-BF_3.Et_2O under similar conditions for converting it into the iodide, but was found to be completely unreactive even on prolonged refluxing (10 hr) in acetonitrile. This further indicated that even normal secondary alcohols are unaffected during iodinations using the above procedure.

The kind of selectivity shown by the above reactions could be explained through HSAB principle.[43] The allylic and benzylic carbons are soft electrophilic centres (soft acids) compared to the non-allylic or non-benzylic carbons, and so the soft nucleophile (base) I^- preferentially attacks these centres when the alcohol group (hard acid) attached to these carbons is activated by the Lewis acid BF_3 (hard acid), leading to formation of the iodides.

II.A.1(iii) Experimental

All melting points are uncorrected and were taken on Fischer-John melting point apparatus. Infrared spectra were recorded on Perkin-Elmer 377, 580 and 1320 spectrometer. Proton NMR spectra were recorded on Varian HA-100 (100 MHz), EM-390 (90 MHz) and Jeol PMX 60 (60 MHz) instruments. Mass spectra were recorded on Jeol JMS-300D Mass spectrometer.

Commercial grade solvents were distilled prior to use. Acetonitrile was dried by storing over anhyd. $CaCl_2$ for at least 24 hr. It was then distilled twice over P_2O_5. Methylene chloride, used for reactions, was dried by distilling over P_2O_5. Tetrahydrofuran was dried by storing over KOH pellets for more than 24 hr, decanting, refluxing and distilling successively over sodium wire and lithium aluminium hydride and finally storing over fresh sodium wire.

Boron trifluoride-etherate (purchased from Fluka) was distilled over CaH_2 under reduced pressure, freshly, prior to use. Sodium iodide (procured from Koch Light Laboratories) was dried in oven at 120°C (and cooled in a desiccator) prior to use.

Preparation of 1-Undecene-3-ol (17) from 1-Undecene (19)

A mixture of 0.40 g (2.6 mmol) 1-undecene, mercuric acetate (1.23 g, 3.90 mmol) and 1.2 ml glacial acetic acid was refluxed

for 12 hr. with vigorous stirring. The reaction mixture was decanted (to remove mercury) and diluted with water (10 ml) and extracted with ether (3 x 10 ml). The combined ether extracts were washed with 10% $NaHCO_3$ solution (3 x 5 ml), brine (5 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent and distillation by a bulb to bulb set up (b.p. 110°C at 1.5 mm) gave 20, 3-acetoxy-1-undecene (yield, 0.47 g, 85%).

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$), 1750 ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$)

PMR (CCl_4), δ (ppm): 1.14-1.84 (m, 17H, $C\underline{H}_3(C\underline{H}_2)_6$), 2.06 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$), 4.3-4.56 (m, 1H, $-C\underline{H}-OCOCH_3$).

A solution of 3-acetoxy-1-undecene 20 (0.39 g, 1.64 mmol) in 1 ml dry methanol was added anhyd. K_2CO_3 (0.43 g, 2.76 mmol) and stirred the suspension vigorously for 2.5 hr at room temperature. The reaction mixture was filtered, evaporated under reduced pressure and the residue neutralized with cold 2N HCl. It was extracted with methylene chloride (3 x 15 ml), washed with brine and dried over anhyd. Na_2SO_4. Evaporation of solvent gave crude 1-undecene-3-ol (17) which was distilled using bulb to bulb set up (yield, 0.25 g, 80%), b.p. 100°C/5.5 mm (lit.[36] 112-114°C/10 mm).

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$), 3500 (br, ν_{O-H}).

PMR ($CDCl_3$), δ (ppm): 0.9 (br, 3H, $-C\underline{H}_3$), 1.1-2.6 (m, 14H, $(C\underline{H}_2)_7$), 2.42 (br,s, 1H, $O\underline{H}$), 3.9-4.1 (m, 1H, $-C\underline{H}-OH$), 4.9-5.84 (m, 3H, vinylic).

Preparation of (E)-2-Undecene-1-ol (18) from 2-Undecene (22)

0.50 g (3.25 mmol) of 2-undecene was converted to 1-acetoxy 2-undecene 23 by the same procedure as before (vide supra) using 1.54 g (4.85 mmol) of mercuric acetate in 1.5 ml gl. HOAc, for 12 hr. (yield, 0.48 g, 70%), b.p. 100°C/1 mm.

IR (thin film), ν_{max} (cm^{-1}): 1645 ($\nu_{C=C}$), 1750 ($\nu_{O-\overset{O}{\overset{\|}{C}}-}$).

0.4 g (1.89 mmol) of 1-acetoxy-2-undecene 23 was hydrolysed as in the case of 20, using 0.44 g of anhyd. K_2CO_3, in 1 ml dry methanol for 2.5 hr to give 2-undecene-1-ol (yield, 0.32 g, 81%), b.p. 100°C/5 mm.

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$), 3400 (br, ν_{O-H}).

PMR ($CDCl_3$), δ (ppm): 0.9 (t, 3H, $-CH_3$), 1.16-2.2 (m, 13H, OH and $-(CH_2)_6$), 3.24-3.6 (m, 2H, $\rangle C=C-CH_2-$), 3.84-4.14 (m, 2H, $CH=CH-CH_2-O-$), 4.90-6.0 (m, 2H, vinylic).

Preparation of 1,5-Dihydroxy-hept-6-ene (30)

0.47 g (10.0 mmol) of NaH (50% dispersion in oil) was washed with petroleum ether to remove oil and then added 5 ml of dry THF to it, and to this stirring suspension was added dropwise a solution of 1.60 g (10 mmol) of diethyl malonate in 5 ml of dry THF. After the addition was over, the mixture was refluxed for 15 min and then a solution of 3-bromo-1-pentene (1.5 g, 10 mmol) in 5 ml. THF, was added and the reaction mixture refluxed for 7 hr. To the reaction mixture was then added 10 ml of water and then extracted with ether (3 x 20 ml). The

ether extract was washed with water (2 x 10 ml), brine (10 ml), and dried over anhyd. Na_2SO_4. Evaporation of the solvent and distillation of crude product, yielded the alkylated product 25 (yield: 2.04 g, 89%), b.p. 122-125°C/10 mm (lit.[38] 130-136°C/ 14 mm).

IR (thin film), ν_{max} (cm^{-1}): 1750 ($\nu_{-\overset{O}{\overset{\|}{C}}-OEt}$), 1650 ($\nu_{C=C}$).

A mixture of the diester 25 (1.5 g, 6.6 mmol), 2.5 ml water 0.5 ml ethanol and 2.0 g KOH was stirred overnight. The solution was concentrated in vacuum, acidified with dil. HCl and extracted thoroughly with ether (3 x 10 ml); Evaporation, after washing the extracts with water (10 ml), brine and drying over anhyd. Na_2SO_4, of the solvent, and recrystallization of the residue with benzene-petroleum ether gave the dicarboxylic acid 26, m.p. 56°C (lit.[38] m.p. 57°C) (yield: 1.02 g, 90%). A mixture of thus obtained dicarboxylic acid 26, 3.0 ml water and 0.5 ml conc. HCl was refluxed for 17 hr., cooled, treated with excess $NaHCO_3$, extracted with ether (2 x 5 ml), acidified the aqueous layer, and reextracted with ether (3 x 10 ml). Evaporation of the latter ether extract, after drying over anhyd. Na_2SO_4 and distillation by a bulb to bulb system, gave the olefinic acid 27, 0.57 g (75%), b.p. 115-120°/10 mm (lit.[38] b.p. 125°C/15 mm).

IR (thin film), ν_{max} (cm^{-1}): 1720 ($\nu_{C=O}^{OH}$), 1650 ($\nu_{C=C}$), 3020 ($\nu_{\overset{O}{\overset{\|}{C}}-OH}$).

0.51 g (4 mmol) of the acid 27 in 1 ml ether at 0°C was then treated with ethereal diazomethane solution (0.01 M), till

the yellow colour of diazomethane persisted and tlc showed absence of acid. The ether was evaporated and the product distilled to give the olefinic ester 28 (yield: 0.54 g, 95%), b.p. 85°C/1 mm (lit.[39] b.p. 106.5°C).

IR (thin film), ν_{max} (cm^{-1}): 1750 (ν_{COOMe}), 1650 ($\nu_{C=C}$).

PMR ($CDCl_3$), δ (ppm): 1.24-1.82 (m, 4H, 2 $C\underline{H}_2$), 1.9-2.42 (m, 4H, $-C\underline{H}_2$ and $C\underline{H}_2-\overset{O}{\overset{\|}{C}}-O-$), 3.58 (s, 3H, $-\overset{O}{\overset{\|}{C}}-O-C\underline{H}_3$), 4.8-5.1 (m, 2H, vinyl), 5.5-6.02 (m, 1H, vinyl).

A mixture of the olefinic ester 28 (0.5 g, 3.5 mmol), gl. HOAc (2.0 ml) and $Hg(OAc)_2$ (1.67 g, 5.25 mmol) was heated at 100°C for 17 hr. Work-up as in the case of 20 and distillation by bulb to bulb method gave the acetoxy ester 29 (yield: 0.57 g, 81%), b.p. 91-92°C/0.3 mm.

IR (thin film), ν_{max} (cm^{-1}): 1750 ($\nu\overset{O}{\overset{\|}{C}}-O-$), 1655 ($\nu_{C=C}$).

PMR ($CDCl_3$), δ (ppm) 1.84 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$), 3.46 (s, 3H, $-\overset{O}{\overset{\|}{C}}-O-C\underline{H}_3$) and 4.86-5.84 (m, 3H, olefinic).

The acetoxy ester 29 (0.5 g, 2.5 mmol) was dissolved in 5 ml of dry ether and a suspension of lithium aluminium hydride (0.19 g, 5 mmol) in 5.0 ml ether was slowly added at 0°C and the reaction mixture stirred for 6 hr. at room temperature. The reaction mixture was then worked up by successive addition of 0.2 ml water, 0.2 ml 15% aq. NaOH solution and then 0.6 ml of water, stirring for additional 10 min., decanting the ether layer and washing the residue twice with ether. The ether layers were combined washed with H_2O, brine and dried only anhyd. Na_2SO_4. Evaporation of the

PMR ($CDCl_3$), δ(ppm): 3.8 (s, 3H, -C-O$\underline{CH_3}$), 4.7 (s, 2H, -O-$\underline{CH_2}$-C(=O)), 7.04-7.72 (m, 4H, aryl), 9.78 (s, H, -C(=O)-$\underline{H}$).

To a suspension of 0.48 g (12.6 mmol) of $LiAlH_4$ in 10 ml ether was added at room temperature, with vigorous stirring, a solution of 1.31 g (6.3 mmol) of 45 in 10 ml ether. The reaction mixture was stirred overnight, and then 10 ml of ethyl acetate was added to it. It was followed by addition of 0.5 ml water, 0.6 ml of 15% NaOH solution and then 1.5 ml of water. After stirring for 15 min. the organic layer was decanted, and the residue washed once with ethyl acetate. The combined organic layers were washed once with water (10 ml), and then with brine (10 ml). Drying over anhyd. Na_2SO_4 and removal of solvent gave the crude diol, which was recrystallized with $CHCl_3$-hexane to give pure combind 38 (yield: 0.85 g, 80%), m.p. 42-43°C.

IR (KBr), ν_{max} (cm^{-1}): 3320 (br, ν_{O-H}).

PMR ($CDCl_3$), δ(ppm): 2.5 (br, s, 2H, 2 O$\underline{H}$), 3.78-4.3 (m, 4H, -O($\underline{CH_2}$)$_2$-OH), 4.6 (s, 2H, Ar-$\underline{CH_2}$), 6.6-7.3 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 168 (100, M^+), 151 (16, M^+-OH).

Anal. for $C_9H_{12}O_2$, Calcd.: C, 64.29; H, 7.14.
Found : C, 64.18; H, 7.06%.

General Procedure for the Conversion of Alcohols to Iodides

To a stirred solution of the alcohol (2.5mmol) and sodium iodide (5mmol) in 8 ml dry acetonitrile was added a solution of

freshly distilled $BF_3.Et_2O$ (5 mmol) in 2 ml dry acetonitrile at 0^oC during 15 min. time. The reaction was then continued till the tlc showed complete conversion of the alcohol (temperature and time for each case is given in Table II.1). The reaction mixture was then poured into 15 ml of ice-cold water and while stirring a 10% solution of sodium thiosulphate was added till the colour of the iodine (liberated during reaction) completely disappeared. It was then extracted with ether (3 x 10 ml), the ether-extracts washed once with water and brine, and then dried over anhyd. Na_2SO_4. Removal of solvent gave the iodide. In all the cases the crude iodides showed single spot on tlc. The solid iodides 14, 40, 44 and 46 were all obtained directly in the crystalline form. They were further purified by recrystallization, while the stable liquid iodide 39, was distilled. The other iodides 16, 24, 21, 31, 41 and 43 which were unstable were purified by flash chromatography (silica gel) using hexane as eluent. The iodide 42, was obtained as a gum which was recrystallized from ether at -40^oC.

The yields and m.p./b.p.s of the various iodides obtained are listed in Table II.1.

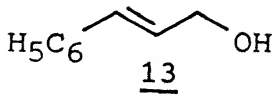
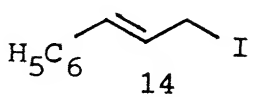
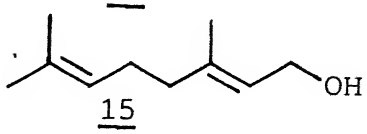
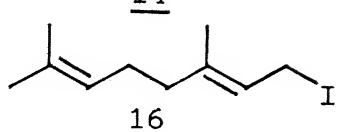
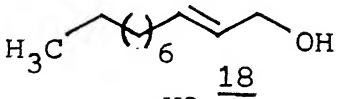
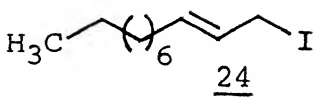
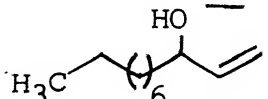
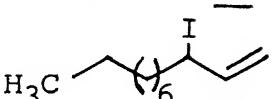
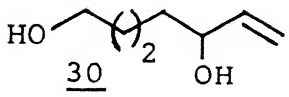
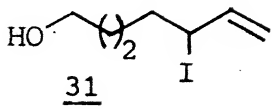
Spectral and Analytical Data of Iodides

Cinnamyl iodide (14)

IR (KBr), ν_{max} (cm^{-1}): 1645 ($\nu_{C=C}$).

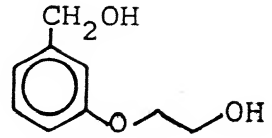
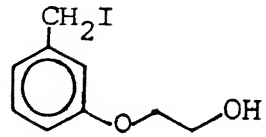
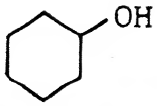
PMR (CCl_4), δ (ppm): 4.0 (d, 2H, J = 7 Hz, $-C\underline{H}_2-I$), 6.1-6.4 (m, 1H, $=C\underline{H}-CH_2$), 6.5 (d, 1H, J = 15 Hz, $Ph-C\underline{H}=$), 7.0-7.3 (m, 5H, aryl).

Table II.1 Conversion of allylic and benzylic alcohols into iodides

Alcohol	Iodide	Time (min)	Temp. (°C)	Yield (%)	m.p.* or b.p. °C / torr (lit. value)
 13	 14	15 15	0 RT	74	56-57* (56.5-57.5)[42]
 15	 16	25	0	70	a
 18	 24	35	0	95	a
 17	 21	45	0	90	a
 30	 31	30	0	71	a
$C_6H_5CH_2OH$ 32	$C_6H_5CH_2I$ 39	25	RT	94	90/8 mm (93/10 mm)[41]
(p-Cl)$C_6H_4CH_2OH$ 33	(p-Cl)$C_6H_4CH_2I$ 40	10 15	0 RT	91	63* (63)[44]

....contd.

Table I.1 (contd.)

Alcohol	Iodide	Time (min)	Temp. (°C)	Yield (%)	m.p.* or b.p. °C/torr (lit. value)
$(m\text{-}Cl)C_6H_4CH_2OH$ 34	$(m\text{-}Cl)C_6H_4CH_2I$ 41	15 15	0 RT	92	a
$(m\text{-}OCH_3)C_6H_4CH_2OH$ 35	$(m\text{-}OCH_3)C_6H_4CH_2I$ 42	20 20	0	92	39* (40)45
$C_6H_5\text{-}CH(OH)\text{-}CH_3$ 36	$C_6H_5\text{-}CH(I)\text{-}CH_3$ 43	15 15	0 RT	93	a
$(o\text{-}SCH_3)C_6H_4CH_2OH$ 37	$(o\text{-}SCH_3)C_6H_4CH_2I$ 44	240	0	98	63*
 38	 46	35	0	91	74*
	No reaction				

Geranyl iodide (16)

IR (thin film), ν_{max} (cm^{-1}): 1655 ($\nu_{C=C}$).

PMR (CCl_4), δ (ppm): 1.60 (s, 3H, $\underline{CH_3}\!>\!C\!=\!CHCH_2\text{-}I$), 1.67 (s, 6H, $(\underline{CH_3})_2C\!=\!CH$), 3.87 (d, 2H, J = 8 Hz, $=CH\text{-}\underline{CH_2}I$), 5.05 (m, 1H, $(CH_3)_2C\!=\!\underline{CH}$), 5.53 (d, 1H, J = 8 Hz, $=\underline{CH}\text{-}CH_2I$), 5.83 (m, 4H, $CH_3\text{-}C\!=\!C\text{-}(\underline{CH_2})_2$).

(E)-Undec-2-enyl iodide (24)

IR (thin film), ν_{max} (cm^{-1}): 1655 ($\nu_{C=C}$).

PMR (CCl_4), δ (ppm): 0.88 (t, 3H, $-\underline{CH_3}$), 1.22-2.22 (m, 12H, $-(\underline{CH_2})_6-$), 3.36 (t, 2H, J = 6 Hz, $C\!=\!C\text{-}\underline{CH_2}\text{-}CH_2-$), 3.74-3.86 (m, 2H, $-\underline{CH_2}I$), 4.92-5.78 (m, 2H, vinylic).

Mass spectrum, m/e (rel. ab.): 280 (7, M^+), 153 (13, M^+-I), 149 (28), 97 (38), 83 (45), 71 (52), 69 (60), 67 (30), 57 (75), 55 (90), 43 (100).

3-Iodoundecene (21)

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$).

PMR (CCl_4), δ (ppm): 0.9 (t, 3H, $-\underline{CH_3}$), 1.16-2.2 (m, 14H, $-(\underline{CH_2})_4$), 3.72-4.0 (m, 1H, $-\underline{CH}\text{-}I$), 4.86-5.54 (m, 3H, vinylic).

5-Iodohept-6-en-1-ol (31)

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$), 3400 (br, ν_{O-H}).

PMR ($CDCl_3$), δ (ppm): 1.3-2.4 (m, 6H, $-(C\underline{H}_2)_3-$), 3.4 (t, 2H, J = 6 Hz, $-OC\underline{H}_2-$), 3.7-4.0 (m, 1H, I-C<u>H</u>-C=C-), 4.88-5.90 (m, 3H, vinylic).

O-Methylthiobenzyl iodide (<u>44</u>)

PMR ($CDCl_3$), δ (ppm): 2.48 (s, 3H, $-SC\underline{H}_3$), 4.44 (s, 2H, $C\underline{H}_2$-I), 6.66-7.12 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 264 (33, M^+), 137 (100, M^+-I) 122 (30).

Anal. for C_8H_9IS, Calcd.: C, 36.37; H, 3.41.
Found : C, 36.35; H, 3.36%.

2-[(m-Iodomethyl)phenoxy]ethanol (<u>46</u>)

IR (KBr), ν_{max} (cm^{-1}): 3350 (br, ν_{O-H}).

PMR ($CDCl_3$), δ (ppm): 2.35 (s, 1H, -O<u>H</u>), 3.83-4.20 (m, 4H, $-O(C\underline{H}_2)-OH$), 4.43 (s, 2H, Ar-CH_2I), 6.77-7.27 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 278 (30, M^+), 153 (100, M^+-I) 136 (32), 135 (41), 95 (60).

Anal. for $C_9H_{11}IO_2$, Calcd.: C, 38.84; H, 3.96.
Found : C, 38.78; H, 3.88%.

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II.A.2 Selective Cleavage of Benzyl Ethers

II.A.2(i) Background

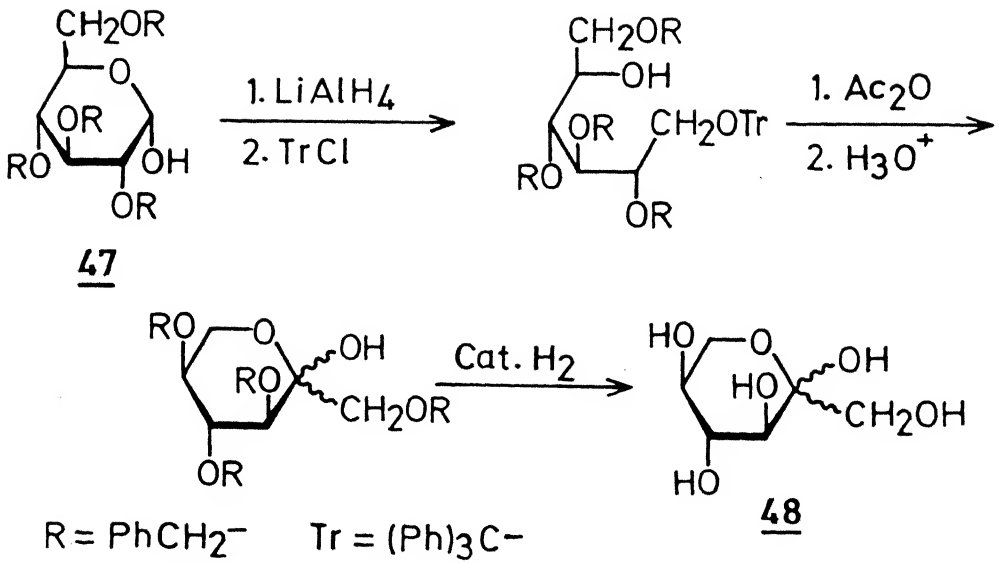
Alcohols undergo a variety of reactions, such as, alkylation, acylation and reaction with other electrophiles, besides being susceptible to oxidations and acid catalysed dehydrations. It is therefore essential to protect the hydroxyl groups, if there are any, at some stage or the other, in a multi-step synthesis of a complex molecule.[1] The benzyl group has been used extensively for protecting hydroxyl groups in the synthesis of several natural products especially carbohydrates,[2] cyclitols[3] and nucleosides.[4] The important features of protection of hydroxyls as benzyl ethers are the following:

(a) The protection can be effected under fairly mild conditions and in good yields.

(b) Benzyl ethers are often crystalline solids and are unaffected by alkali; they are stable enough to withstand acidic hydrolytic conditions normally required for the removal of isopropylidene and benzylidene groups. Benzyl ethers are also stable to a large number of reagents, such as lithium aluminium hydride and lead tetraacetate.

(c) They can readily be cleaved selectively under mild conditions by a variety of methods.

An example of the use of benzyl protecting group in carbohydrate chemistry, is in the conversion of 2,3,4,6-tetra-O-benzyl-D-glucose (47) into L-sorbose(48)(Scheme II.14a).[5]



47

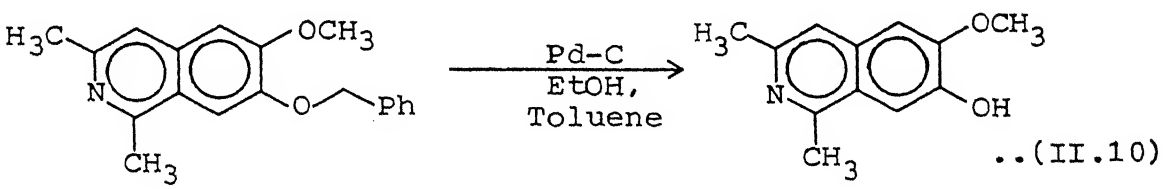
48

SCHEME II·14a

Although several reagents are available for the cleavage of benzyl ethers,[6] not all of them are selective for benzyl ethers, as other types of ethers may also be cleaved by the same reagent. The methods presently available for the cleavage of benzyl ethers may be broadly categorized as follows: (a) Reductive methods, which include catalytic hydrogenation and use of sodium-ammonia. (b) Acidic methods, which include Lewis acid-nucleophile combinations. (c) Basic methods, which include organoalkali metal amide reagents. (d) Oxidative methods. (e) Miscellaneous reagents which do not come in the above mentioned categories. A brief review of these methods is presented below.

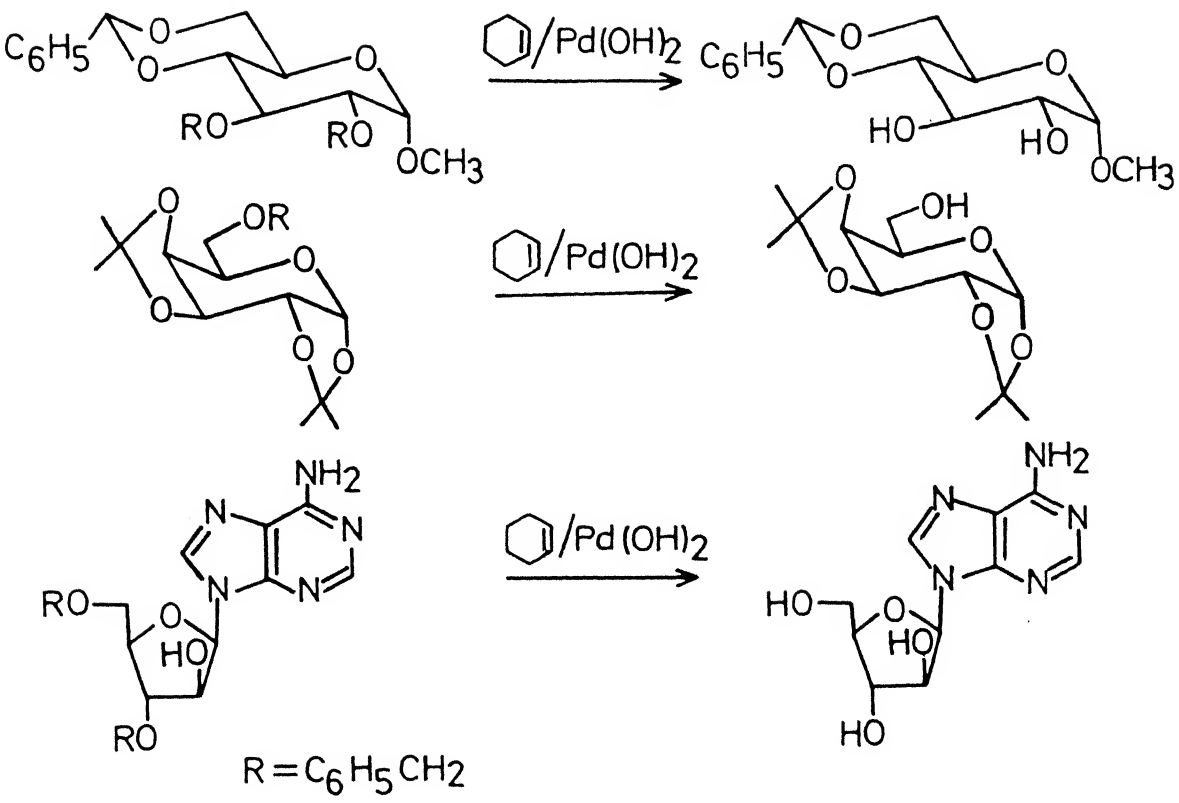
(a) Reductive Methods

One of the classical methods which is commonly used for the cleavage of benzyl ethers is by catalytic hydrogenation,[7] which employs mild conditions. Benzyl, benzhydril and trityl groups are also cleaved by hydrogenolysis in the presence of a trace of an acid. The catalysis generally used include Pd-C, Pt and Raney nickel. An example is given in Eqn. II.10 which indicates that methyl ethers are not affected during hydrogenolysis,[7a]



..(II.10)

A recent, interesting development, is the hydrogenolysis by transfer hydrogenation[8] using 20% $Pd(OH)_2$ on carbon and cyclohexene as the hydrogen donor. The noteworthy features of this method are: (a) benzyl ethers can be cleaved in the presence of a benzylidene acetal, (b) esters (acetates, benzoates, sulphonates), ethers such as methoxyethoxymethyl, methoxymethyl, tetrahydropyranyl, acetals and glycoside groups are all unaffected, indicating the potential of this method in carbohydrate chemistry, (c) even difficult substrates like nucleoside benzyl ethers can also be readily cleaved. A few examples are illustrated in Scheme II.14b. The only drawback with this method is that olefins get reduced[8b] under the reaction conditions.

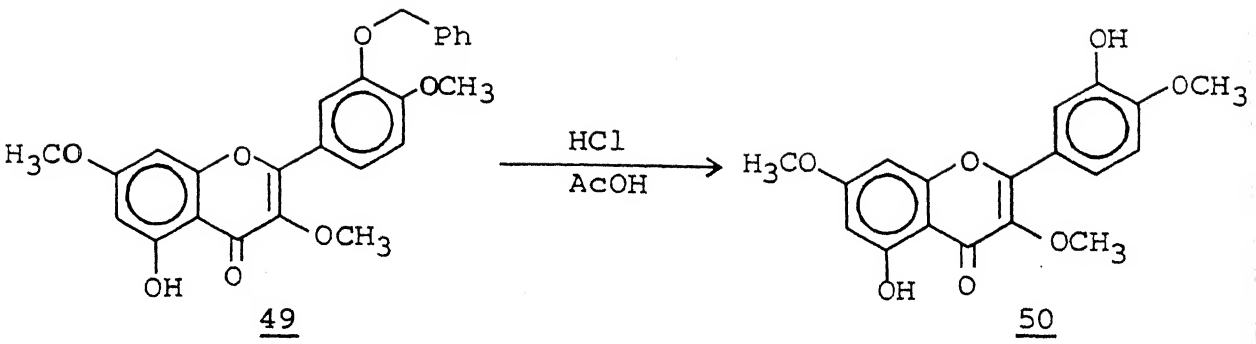


SCHEME II-14 b

Benzyl ethers have also been reductively cleaved by sodium in liquid ammonia.[9] Diaryl and alkyl aryl ethers are also cleaved by this method, but unlike catalytic hydrogenation, isolated double bonds are not reduced.[10]

(b) Acidic Methods

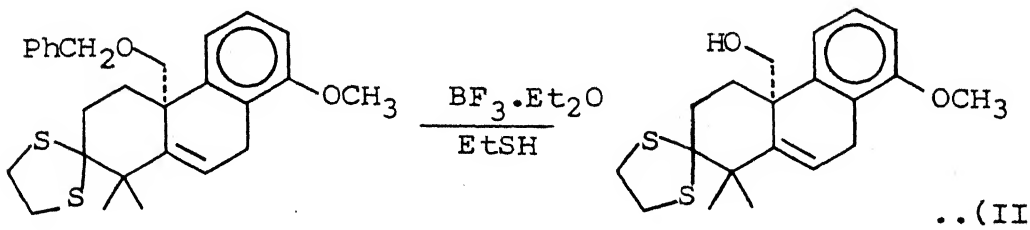
Hydrochloric acid[11] has been used to cleave benzyl ethers. It also cleaves benzhydril, t-butyl, allyl, trityl and naphthyl methyl ethers, but does not cleave certain types of aryl methyl ethers. Thus, selective cleavage of benzyl ether of 3'-benzylayanin (49) to flavanone derivative 50 was affected with conc. HCl in the presence of acetic acid(Eqn.II.11)



49 50

Trifluoroacetic acid[12] has been used to selectively cleave aryl benzyl ethers (provided the aromatic ring has either meta- or ortho-para directing groups) without affecting methyl ethers. It also cleaves benzhydril and trityl groups. However, in the case of fluorophenyl benzyl ethers, cleavage followed by ring benzylation has been reported.

Benzyl ethers could also be cleaved by using a combination of a Lewis acid and a nucleophile. Thus, a combination of boron trifluoride etherate and ethane thiol or ethane dithiol provides an efficient system for the selective cleavage of benzyl ethers[13] in the presence of aryl methyl ethers (Eqn. II.12).



..(II.12)

The cleavage of C-O bond by this system is based on the balance between the coordination of hard acid with oxygen atom and the nucleophilic attack of soft nucleophile at the carbon atom.

Alkyl methyl ethers and aryl methyl ethers are also cleaved,[14] but very slowly when compared to benzyl ether. The rate of cleavage of both aliphatic and aromatic methyl ethers is considerably enhanced when aluminium chloride or aluminium bromide is used, instead of borontrifluoride etherate, with a thiol,[15] With this system there is no longer much descrimination in the rates of cleavage of the three types of ethers, and hence selectivity towards benzyl ethers in lost.

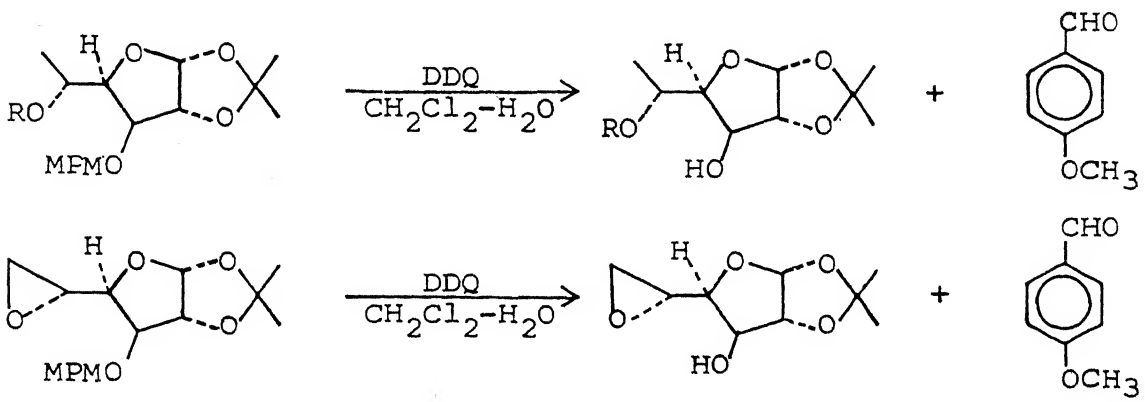
(c) Basic Methods

Certain organoalkali metal amides like sodium N-methylanilide[16] and sodium piperidide[17] have been reported to cleave benzyl ethers. While sodium N-methylanilide (prepared from N-methylaniline and sodium hydride in xylene-HMPT) in HMPT cleaves aryl benzyl ether and aryl methyl ethers, sodium piperidide (prepared from sodamide and piperidine) in piperidine, cleaves diaryl ethers as well. With these reagents aryl methyl ethers are cleaved more readily than aryl benzyl ethers. The full scope of these reagents for the cleavage of ethers has not been investigated.

(d) Oxidative Methods

2,3-Dichloro-5,6-dicyano-1,4-quinone (DDQ)[18] in CH_2Cl_2-H_2O is a reagent which cleaves p-methoxy benzyl ethers at room temperature. Normal benzyl ether, alkyl ethers and arylmethyl ethers are unaffected under these conditions. Other usual protecting groups like isopropylidene, methoxymethyl,

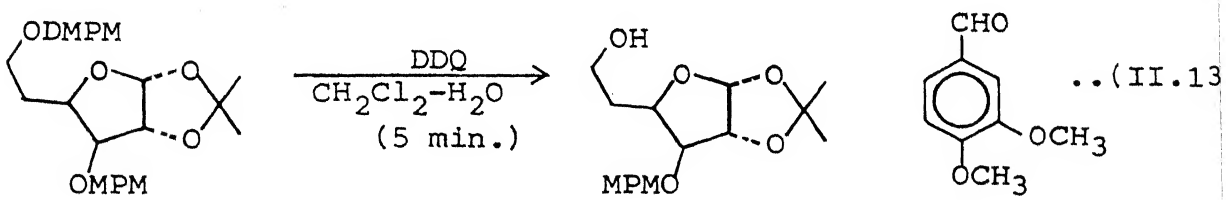
benzyloxy methyl, THP, acetyl and functional groups like epoxide, double bond and ketone, are all unaffected under the mild oxidative conditions of DDQ (Scheme II.15)



R = $C_6H_5CH_2$, MPM = p-methoxy phenyl

SCHEME II.15

Interestingly, 3,4-dimethoxy benzyl ethers (DMPM) can be cleaved selectively in the presence of p-methoxy benzyl ethers (MPM), because of the lower oxidation potential of the dimethoxy benzyl group (Eqn. II.13):



..(II.13

Catalytic amount of ceric ammonium nitrate,[19] with one molar equivalent of sodium bromate has been found to cleave benzyl ethers, but methyl, ethyl and silyl ethers are also cleaved under these oxidative conditions and hence this method offers little advantage over DDQ method.

Stable cation radical salts[20] derived from tris[p-bromophenyl]amine (A) have been used to oxidatively cleave MPM

ethers under mild conditions. The mechanism of the reaction is shown in Scheme II.16a:

$$[p\text{-}BrC_6H_4]_3N^{\ddagger}\ SbCl_6^- + R'\text{-}O\text{-}CH_2\text{-}R^2 \rightleftharpoons [p\text{-}BrC_6H_4]_3N + [R'\text{-}O\text{-}CH_2\text{-}R^2]^{\ddagger}$$

(A)

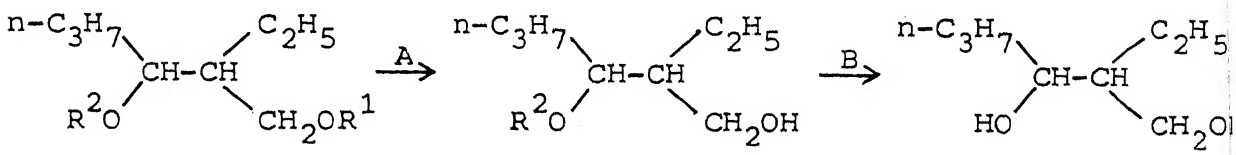
$$[R'\text{-}O\text{-}CH_2\text{-}R^2]^{\ddagger} + H_2O \rightleftharpoons [R'\text{-}O\text{-}\dot{C}H\text{-}R^2] + H_3O^+$$

$$[R'\text{-}O\text{-}\dot{C}H\text{-}R^2] + [p\text{-}BrC_6H_4]_3N^{\ddagger}\ SbCl_6^- \rightleftharpoons [R'\text{-}O\text{-}\overset{+}{C}H\text{-}R^2] + [p\text{-}BrC_6H_4]_3N$$

$$[R'\text{-}O\text{-}\overset{+}{C}H\text{-}R^2] + H_2O \rightarrow R^2\text{-}CHO + R'\text{-}OH$$

SCHEME II.16a

Using cation radicals with higher redox potential, like that derived from [bis-(2,4-dibromophenyl)]-p-bromophenylamine (B), simple benzyl ethers could also be cleaved (Scheme II.16 b):



$R^1 = (p\text{-}CH_3O)C_6H_4CH_2\text{-}$; $R^2 = C_6H_5CH_2\text{-}$

SCHEME II.16b

(e) Miscellaneous Methods

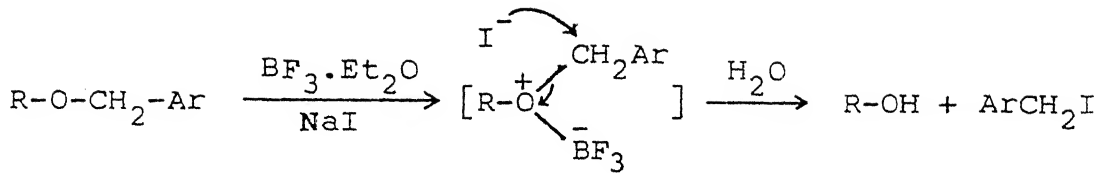
Several other reagents have been reported to cleave benzyl ethers. Diphenyllithium phosphide has been claimed to cleave aryl methyl and aryl benzyl ethers selectively

without affecting dialkyl ethers.[21] Recently several silicon based reagents have been reported, which can cleave ethers under mild conditions. Iodotrimethylsilane, developed independently by Jung et al.[22] and Olah et al.[23] has been shown to cleave all types of ethers. Olah et al.[24] have shown that iodotrimethylsilane can be conveniently and efficiently generated *in situ* by reacting sodium iodide with chlorotrimethylsilane in acetonitrile. Bhatt et al.[25] have shown that the less expensive iodotrichlorosilane (generated *in situ* from tetrachlorosilane-sodium iodide) cleaves ethers with equal efficiency as iodotrimethylsilane. The latest addition to the silane based reagents is the trichloromethylsilane/sodium iodide system,[26] which again cleaves all types of ethers at ambient temperature.

The reagents, methylthio, phenylthio or 1,2-ethanedithiobis(trimethylsilane) in combination with zinc iodide and tetrabutylammonium iodide effect cleavage of methyl and benzyl ethers.[27] This reagent system takes into account the relatively large difference in bond energies between S-Si and O-Si. The high O-Si bond energy provides the activation for the attack of nucleophile, and the concomittant cleavage of the C-O bond. This is also the case with the other silicon reagents discussed earlier.

II.A.2(ii) Present Work

In the first part of this chapter (Sec. II.A.1(i)) the results obtained by us by utilizing NaI-BF_3.Et_2O as a reagent system to bring about selective conversion of allylic and benzylic alcohols into iodides have been presented. It was concluded from the study that the success of selective iodination of the allylic and benzylic alcohols is due to the balance between the coordination of the hard acid (BF_3.Et_2O) with the hard basic oxygen atom of alcohol and nucleophilic attack of a soft nucleophile (iodide ion) on the soft electrophilic benzylic or allylic carbon atom. It was therefore anticipated by analogy that benzyl ethers under similar conditions should be easily cleaved to the corresponding alcohols by the NaI-BF_3.Et_2O reagent system. In the background section of the present part a literature survey about the cleavage of benzyl ethers is presented. It appears that although there are a number of reagents available to bring about such a reaction, there is still a need to introduce newer reagents/reagent systems which could be operative under milder conditions leading to high yields of the cleavage products with high degree of selectivity. The present study was undertaken with this view in mind and we have found that benzylic ethers are selectively cleaved under extremely mild conditions with the NaI-BF_3.Et_2O reagent system. A plausible mechanism for the cleavage reaction is illustrated in Scheme II.17



SCHEME II.17

A set of ethers chosen for the study are listed in Table II. In general, the reactions were carried out first at 0°C and then at room temperature (wherever required), and yields of the cleavage products ranged from 75-94%. When dibenzyl ether (51) was reacted with $BF_3.Et_2O$ and NaI in 1:1:1 molar equivalent ratio at 0°C for one hr and at RT for 0.5 hr, 50% of the starting material was recovered unreacted along with 47% of benzyliodide (52). But when the ether 51, $BF_3.Et_2O$ and NaI in the molar ratio 1:2:2.4 were used benzyliodide was the only product obtained in 90% yield. In both the cases no benzyl alcohol was obtained clearly indicating that the benzyl alcohol formed was immediately converted to the iodide under the reaction conditions. However, cyclohexyl benzyl ether (53), 2-methylcyclohexyl benzyl ether (54) and 4-phenylcyclohexyl benzyl ether (55) on reaction with NaI and $BF_3.Et_2O$ (in the molar ratio 1:1.25:1.25, respectively), underwent smooth cleavage to give the corresponding alcohols 56, 57 and 58 in 75%, 85% and 94% yields, respectively. These examples indicate that benzyl ethers derived from simple alphatic alcohols can be readily cleaved with this reagent system. In yet another example, (3-phenylthio)benzyloxypropane (59), which contained a benzyl ether along with a phenylthio group, a two-fold excess of both $BF_3.Et_2O$ and NaI were required (the reaction time being 1 hr

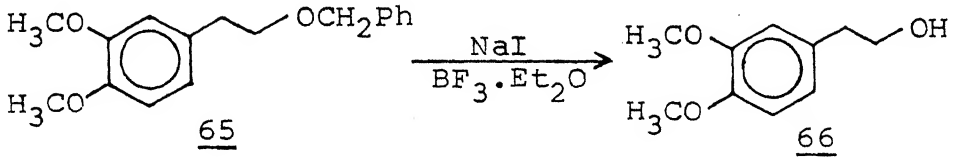
at 0°C, followed by 7 hr reaction at room temperature), to give the alcohol 60 in 80% yield, b.p. 156°C/8 mm (lit.[28] b.p. 134-135°C/2 mm).

We then chose two examples of benzyl ethers viz., 61 and 62 derived from phenols. Thus, phenyl benzyl ether (61) required a longer time (5 hr at 0°C and then 16 hr at room temperature) for the completion of reaction, whereas 2-naphthyl benzyl ether (62) reacted completely during 1 hr at 0°C followed by 2 hr at room temperature, to yield 85% and 90% of the phenol (63) and β-naphthol (64), respectively.

The above experiments clearly indicate a retardation of the reaction rate on going from saturated aliphatic benzyl ethers to phenolic benzyl ethers. This is expected since the availability of the lone pair of electrons of ether oxygen for coordinati with BF_3 is reduced due to their participation with the aromatic

In order to compare the reactivity of benzyl ethers with other ethers reactions were carried out with a set of ethers 65, 67 and 69 (see Table II.2). 1-Benzyloxy-2-[1,2-dimethoxypheny ethane (65) was prepared in 85% yield by reacting the corresponding alcohol 66 with benzyliodide in the presence of NaH in refluxing THF. The IR spectrum of this compound showed peak at 1110 cm (ν_{C-O}), and ^{1}H NMR spectrum showed absorptions at δ 2.7 (t, 2H, J = 7 Hz, -C$\underline{H}_2$-O-), 3.5 (t, 2H, J = 7 Hz, -CH$_2$-C$\underline{H}_2$-O-), 3.64 (s, 6H, 2-O-C$\underline{H}_3$'s), 4.32 (s, 2H, O-C$\underline{H}_2$Ph), 6.5 (s, 3H aryl) and 7.08 (s, 5H, aryl).

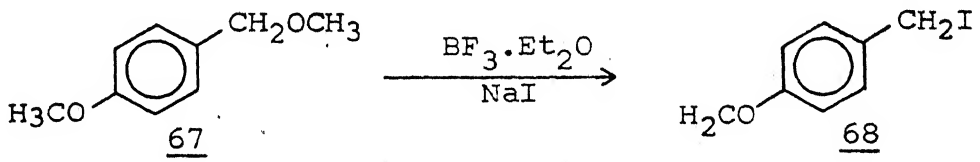
Thus, compound 65, when treated with NaI-$BF_3.Et_2O$ in the ratio 1:1.25:1.25 first at 0°C for 1 hr and then for 1.5 hr at room temperature, led to the formation of the 2-(3,4-dimethoxyphenyl)-ethanol (66) (Eqn. II.14) in 90% yield. IR spectrum of this



.. (II.14)

alcohol showed absorption at 3300 cm^{-1} (ν_{-OH}), and its ^1H NMR spectrum indicated peaks at δ 2.62 (t, 2H, J = 7 Hz, Ar-CH_2), 3.6 (s, 6H, 2-OCH_3's) and at 6.56 (s, 3H, aromatic). It was clearly seen from its ^1H NMR spectrum that the two methoxy groups were intact and the benzyl ether was selectively cleaved, under the reaction conditions.

Further examples taken by us in this study were the two substituted benzyl ethers 67 and 69. Thus, 4-methoxybenzyl methyl ether (67) was found to undergo cleavage at 0°C for 2 hr to give the 4-methoxy benzyliodide 68 in 94% as a low melting solid (lit.[29] m.p. 27°C) (Eqn. II.15). The arylmethoxy-(4-methoxyphenyl) group remained once again intact under the reaction conditions as evidenced by its ^1H NMR spectrum which showed

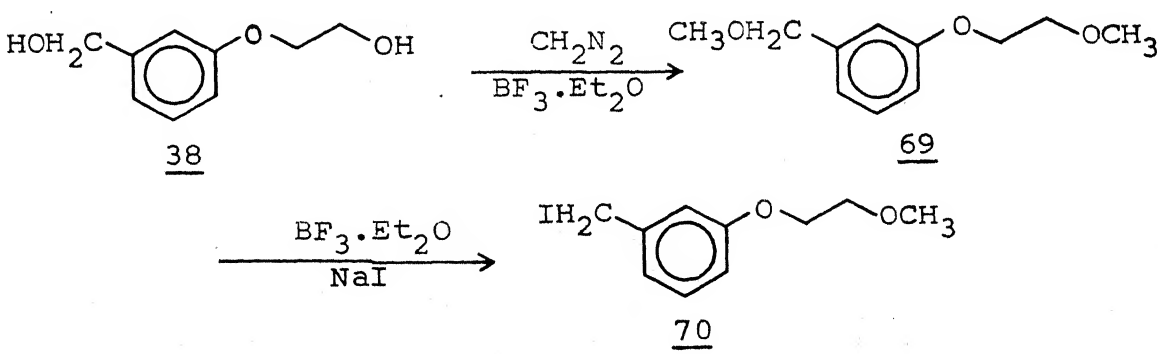


.. (II.15

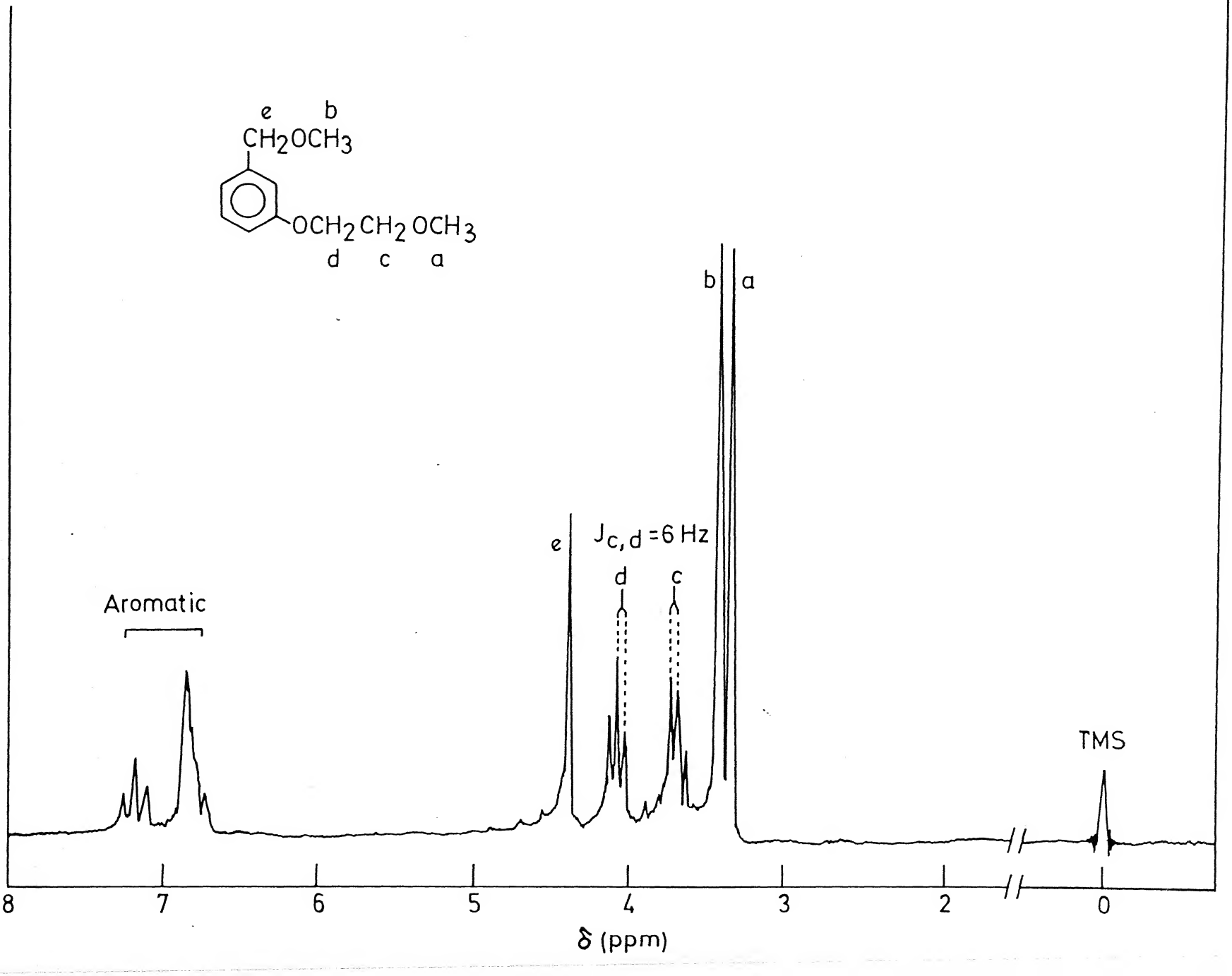
absorptions at 3.6 (s, 3H, $-OCH_3$), 4.24 (s, 2H, CH_2I) and 6.52-7.16 (m, 4H, aryl).

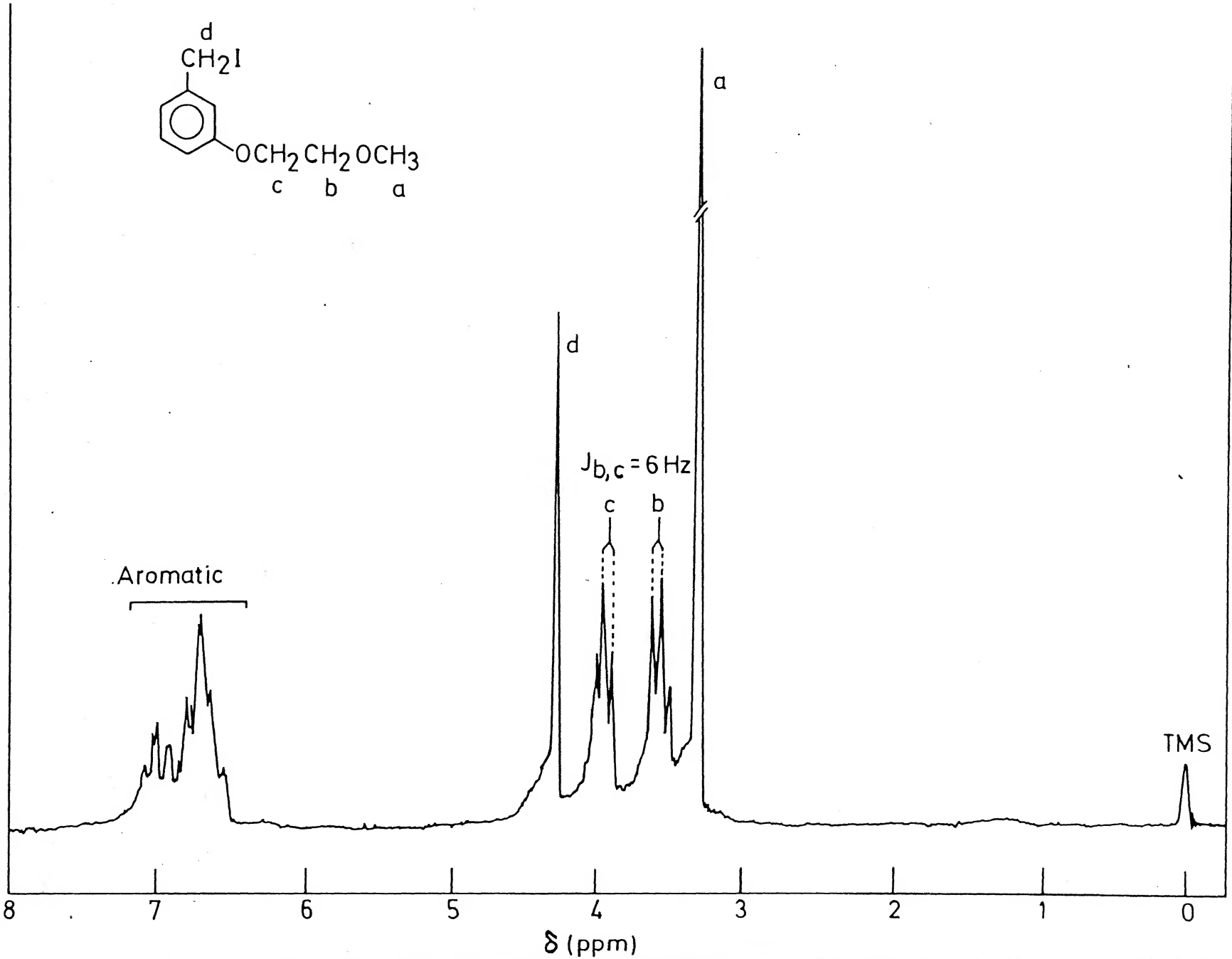
An interesting typical example 69 (see Table II.2) having all the three types of ether linkages viz., aryl ether, aliphatic methyl ether and the benzyl ether was chosen for our study. It was prepared by reacting the diol 38 with CH_2N_2 in the presence of $BF_3.Et_2O$ at 0°C in 90% yield, b.p. 140°C/0.5 mm. Its ^1H NMR spectrum showed absorptions at δ 3.3 (s, 3H, CH_2CH_2-O-CH_3), 3.36 (s, 3H, $ArCH_2OCH_3$), 3.66 (t, 2H, $-CH_2CH_2OCH_3$), 4.04 (t, 2H, $-OCH_2CH_2-$), 4.32 (s, 2H, $ArCH_2-$), 6.56-7.2 (m, 3H, aryl) and mass spectrum showed M^+ peak at 196. This compound 69, when reacted with $BF_3.Et_2O$ and NaI in the ratio 1:2:2 molar ratio, at 0°C for 2 hr, the iodide 70 was the only product formed in the reaction (Scheme II.18), and was isolated in 94% yield. Its IR spectrum showed absence of -OH group and ^1H NMR spectrum showed absorptions at δ 3.3 (s, 3H, $-OCH_3$), 3.63 (t, 2H, $-CH_2-OCH_3$, J = 6 Hz), 4.01 (t, 2H, Ar-OCH_2, J = 6 Hz), 4.3 (s, 2H, $ArCH_2I$), 6.57-7.4 (m, 4H, aromatic). Mass spectrum showed M^+ at 292.

From the spectral data it is apparent that only the benzylic ether linkage is cleaved, while the aryl alkyl ether and aliphatic methyl ether linkages are unaffected under the reaction conditions.



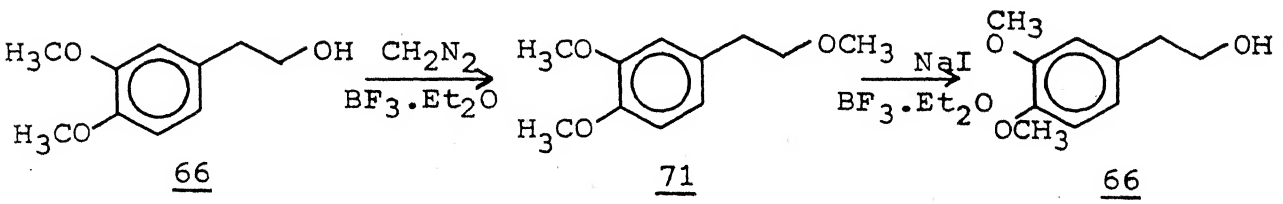
SCHEME II.18


e b
CH2OCH3
OCH2CH2OCH3
d c a
b a
e
Jc,d =6 Hz
d
c
Aromatic
TMS
8
7
6
5
4
3
2
0
δ (ppm)


d
CH2I
OCH2CH2OCH3
c b a
a
d
Jb,c = 6 Hz
c
b
Aromatic
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

The examples studied so far clearly indicated that the reactivity of benzyl ethers is extremely high as compared to arylmethyl (alkyl) ethers and aliphatic methyl ethers. This method could thus be used for the selective cleavage of benzyl ethers in the presence of other ethers.

In order to compare the reactivity of aliphatic methyl ethers versus aryl methyl ethers, the compound 2-(3,4-dimethoxyphenyl)ethyl methyl ether 71 was chosen. This was prepared by diazomethane treatment of the alcohol 66 in the presence of $BF_3.Et_2O$, in 92% yield, b.p. 135°C/0.5 mm. Its IR spectrum showed absence of -OH group and ^1H NMR spectrum showed absorptions at δ 2.58 (t, 2H, Ar-CH_2, J = 6 Hz), 3.22 (s, 3H, -CH_2-O-CH_3), 3.4 (t, 2H, -CH_2-OCH_3), 3.74 (s, 3H, Ar-OCH_3), 6.54 (s, 3H, aromatic). Mass spectrum showed M^+ peak at 196. Upon treatment of 71 with $BF_3.Et_2O$ and NaI in molar ratio 3:3 at room temperature for 72 hr 64% of the alcohol 66 was obtained whose spectral characteristic were the same as that of 2-(3,4-dimethoxyphenyl)ethanol, clearly indicating that the aliphatic methyl ether was cleaved, the aryl methyl ethers once again remaining unaffected under the reaction conditions (Scheme II.19).

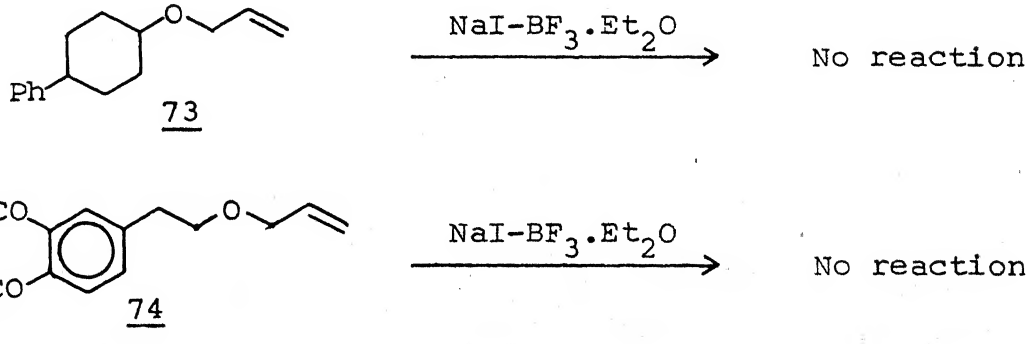


SCHEME II.19

The relative reluctance of aryl methyl ethers to undergo cleavage, in comparison to aliphatic methyl and benzyl ethers appears to be useful if any selectivity is to be observed. Furthermore, the observation that the rate of cleavage of benzyl ethers is higher than that of aliphatic methyl ethers is also beneficial from the selectivity point of view.

Finally, in order to test whether aryl methyl ethers do undergo cleavage at all or not, anisole(72) was reacted with NaI-$BF_3.Et_2O$ at room temperature and was found to form phenol(63) after 96 hr in only 64% yield, the unreacted anisole being recovered.

A careful examination of the relative reactivities with different kinds of ethers as studied above does indicate that the reactivity order for ether cleavage with NaI-$BF_3.Et_2O$ reagent system is benzyl ether > aliphatic methyl ether > aryl methyl ether. Such a reactivity order seems to be again based on the HSAB principle, which was observed in the selective conversion of benzylic and allylic alcohols into the corresponding iodides (cf. A.1(i) of this chapter). Surprisingly, however, no reaction of allyl ethers 73 and 74 was observed under similar conditions of the reaction (Scheme II.20).



73

74

SCHEME II.20

The study of ether cleavage is somewhat comparable to the one reported by Fujita et al.,[13] where they had used EtSH (or $HSCH_2CH_2SH$)-$BF_3.Et_2O$ combination, instead of NaI-$BF_3.Et_2O$ used in our study. However, the use of EtSH (or $HSCH_2CH_2SH$) is not convenient, as the byproduct obtained in their case cannot be recycled unlike the present case, where the benzyl iodide formed could be recycled for the preparation of benzyl ethers. Thus, the present method is more advantageous, and also the reactivity of NaI-$BF_3.Et_2O$ combination is found to be much higher than that of thiol-$BF_3.Et_2O$ combination.

II.A.2(iii) Experimental

The details regarding the instruments and the reagents used are the same as described in Sec. II.A.1(iii). Also the solvents used were dried as described in the same section.

Tetrahydrofuran (THF) used as solvent for the preparation of some of the benzyl ethers was dried by storing over KOH pellets for 24 hr., decanting, refluxing successively over sodium wire and lithium aluminium hydride and finally storing over fresh sodium wire.

Preparation of Starting Materials

The aryl benzyl ethers viz., phenyl benzyl ether (61) and naphthyl benzyl ether (62) were prepared by the procedure described in the literature.[30] Dibenzyl ether (51) was also prepared by the literature procedure.[31]

The benzyl ethers 53, 54, 55, 59 & 65 (refer Table II.2) were prepared from their corresponding alcohols according to the procedure described below:

To a stirred mixture of NaH (0.01 mol) in 10 ml dry THF was slowly added the alcohol (0.01 mol), and the mixture refluxe for 15 min. Benzyl iodide (0.01 mol) was then added at room tempe rature and mixture was again refluxed for 10 hr. The reaction mixture was then diluted with 20 ml solvent ether and washed with

water (2 x 5 ml), brine (5 ml) and then dried the organic layer over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography (silica gel, 1:1 benzene-hexane as eluent) gave the pure benzyl ether in about 80% yield.

Preparation of m-(2-methoxyethyloxy)benzyl methyl ether (69)

To a solution of 1.54 g (0.01 mol) of diol 38 (prepared according to the procedure described in Sec. II.A.1(iii)) in 5 ml dry dichloromethane at 0°C was added 0.13 ml (0.001 mol) of $BF_3.Et_2O$. An etheral solution of diazomethane (1.0 M) was slowly added dropwise with shaking till there was no N_2 evolution and the yellow colour of diazomethane persisted. The solvent was then evaporated and the product distilled under reduced pressure to get the pure compound 69 (yield: 1.64 g, 90%), b.p. 140°C/ 0.5 mm.

PMR ($CDCl_3$), δ (ppm): 3.30 (s, 3H, CH_2CH_2-O$\underline{CH_3}$), 3.36 (s, 3H, Ar-$CH_2O\underline{CH_3}$), 3.66 (t, 2H, J = 6 Hz, -$CH_2\underline{CH_2}OCH_3$), 4.04 (t, 2H, J = 6 Hz, -O$\underline{CH_2}CH_2$-), 4.32 (s, 2H, Ar-$\underline{CH_2}$-O-), 6.56-7.20 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 196 (38, M^+), 166 (7), 138 (13), 120 (11), 107 (16), 106 (13), 89 (20), 59 (100).

Anal. for $C_{11}H_{16}O_3$, Calcd.: C, 67.35; H, 8.16.
Found : C, 67.30; H, 8.14%.

Preparation of 2-(3,4-dimethoxyphenyl)ethyl methyl ether (71) and p-Methoxybenzyl methyl ether (67)

The two ethers were prepared from their corresponding alcohols 66 and p-methoxybenzyl alcohol (0.01 mol in each case) by the same procedure as described above for the preparation of 69 (yields of 71 and 67 are 92% and 90%, respectively).

PMR of 71 ($CDCl_3$), δ (ppm): 2.58 (t, 2H, J = 6 Hz, $ArC\underline{H}_2$), 3.22 (s, 3H, $-CH_2-O-C\underline{H}_3$), 3.40 (t, 2H, J = 6 Hz, $-C\underline{H}_2-OCH_3$), 3.68 (s, 3H, $Ar-OC\underline{H}_2$), 3.74 (s, 3H, $Ar-OC\underline{H}_3$), 6.54 (s, 3H, aryl).

PMR of 67 ($CDCl_3$), δ (ppm): 3.35 (s, 3H, $ArCH_2-OC\underline{H}_3$), 3.71 (s, 3H, $Ar-OC\underline{H}_3$), 6.6 (q, 4H, aryl).

General Procedure for the Cleavage of Ethers

To a stirred solution of the ether (3 mmol) and anhydrous NaI at 0°C was added slowly a solution of freshly distilled $BF_3.Et$ (molar equiv. of NaI and $BF_3.Et_2O$ used in each case are given in Table II.2) during 10 min. The mixture was stirred at 0°C and if required at room temperature for periods indicated in Table II. The reaction mixture was poured into ice cold water (20 ml), treated with a few drops of 10% hypo solution (to decolourize any iodine liberated during reaction), and then extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with water (2 x 5 ml) followed by brine (5 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent and separation by column chromatography over silica gel (with hexane and then

chloroform) gave benzyl iodide and the alcohols which were further purified by distillation or recrystallization.

The benzyl ethers 53, 54, 55, 59, and 66 were cleaved and purified as described above.

In case of the aryl benzyl ethers 61 & 62 and anisole (72) the phenols obtained were separated directly by extracting the organic layer with 10% aqueous NaOH (2 x 5 ml). The aqueous extract was cooled, acidified with conc. HCl, saturated with solid sodium chloride and extracted with ether (3 x 10 ml). Drying and evaporation of the solvent gave the pure phenols (refer Table II.2

In case of ethers 67, 69 and 51, the only isolable products obtained were the iodides 68, 70 and 52, respectively which were purified by flash chromatography (silica gel using hexane and 5% ether as eluent).

The ether 71 gave only the alcohol 66, which was purified by column chromatography (silica gel, benzene as eluent).

The boiling points/m.ps. of the cleaved products and their yields are given in Table II.2. The physical and spectral charac teristics of the alcohols obtained from cleavage of benzyl ethers 53, 54, 55, 59 and 65 were identical with those of the starting alcohols from which these ethers were obtained.

Spectral characteristics of m-(2-methoxyethyloxy) benzyl-iodide (70).

PMR ($CDCl_3$), δ (ppm): 3.30 (s, 3H, $-CH_2CH_2-O\underline{CH}_3$), 3.63 (t, 2H, J = 6 Hz, $-\underline{CH}_2-OCH_3$), 4.01 (t, 2H, J = 6 Hz, $Ar-O\underline{CH}_2-$), 4.3 (s, 2H, $Ar-\underline{CH}_2-I$), 6.57-7.40 (m, 4H, aryl).

Mass spectrum, m/e (rel. ab.): 292 (5, M^+), 165 (100 M^+-I), 133 (21), 107 (26), 90 (21).

Anal. for $C_{10}H_{13}IO_2$, Calcd.: C, 41.1; H, 4.45.

Found : C, 41.21; H, 4.52%.

Table II.2 Cleavage of Ethers Using NaI-$BF_3.Et_2O$

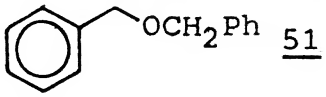
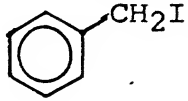
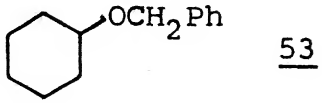
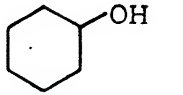
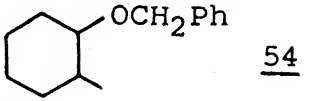
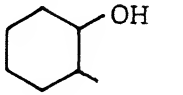
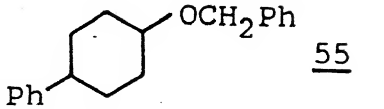
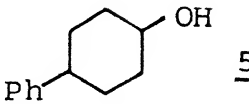
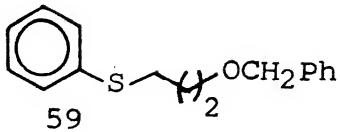
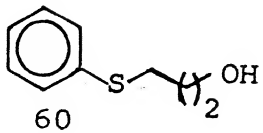
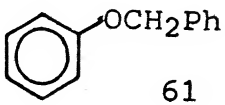
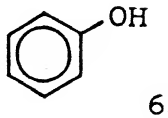
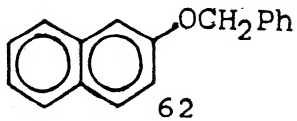
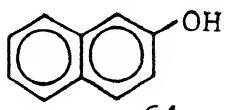
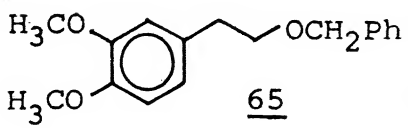
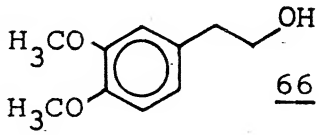
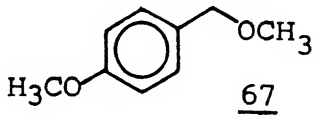
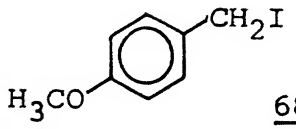
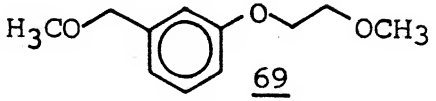
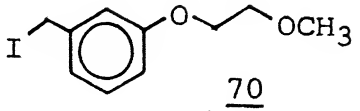
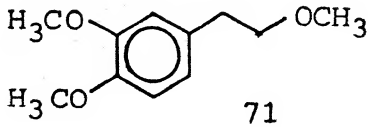
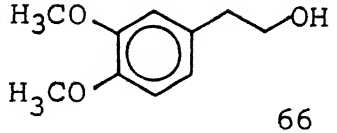
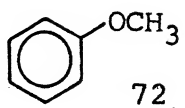
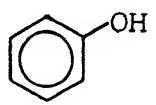
Ether	Product	Mol. equivs. $BF_3.Et_2O$	Mol. equivs. NaI	Conditions temp/time	Yield (%)	m.p.* or b.p. °C/torr (lit. value)
1	2	3	4	5	6	7
 51	 52	1.0	2.4	0°C/1 hr RT/30 min	90	94/10 (93/10)[33]
 53	 56	1.25	1.25	0°C/45 min RT/15 min	75	160 (161)[32]
 54	 57	1.25	1.25	0°C/45 min RT/15 min	85	78/20 (59/10)[32]
 55	 58	1.25	1.25	0°C/30 min	94	76* (76-77)[32]
 59	 60	2.0	2.0	0°/1 hr RT/7 hr	80	156/8 (134/2)[28]
 61	 63	1.4	1.4	0°C/5 hr RT/16 hr	85	42* (43)[32]
 62	 64	1.4	1.4	0°C/1 hr RT/2 hr	90	122-23 (123)[32]

Table II.2 (contd.)

1	2	3	4	5	6	7
 65	 66	1.25	1.25	0°C/1 hr RT/1.5 hr	90	42* (42-43)[34]
 67	 68	1.4	1.4	0°C/2 hr	94	26* (27)[29]
 69	 70	2.0	2.0	0°C/2 hr	94	a
 71	 66	3.0	3.0	0°C/1 hr RT/72 hr	64	41-42 * (42-43)[34]
 72	 63	2.5	2.5	0°C/1 hr	64[b]	42-43* (43)[32]

a, obtained as oil which decomposes on distillation.

b, 32% of unreacted 72 was recovered.

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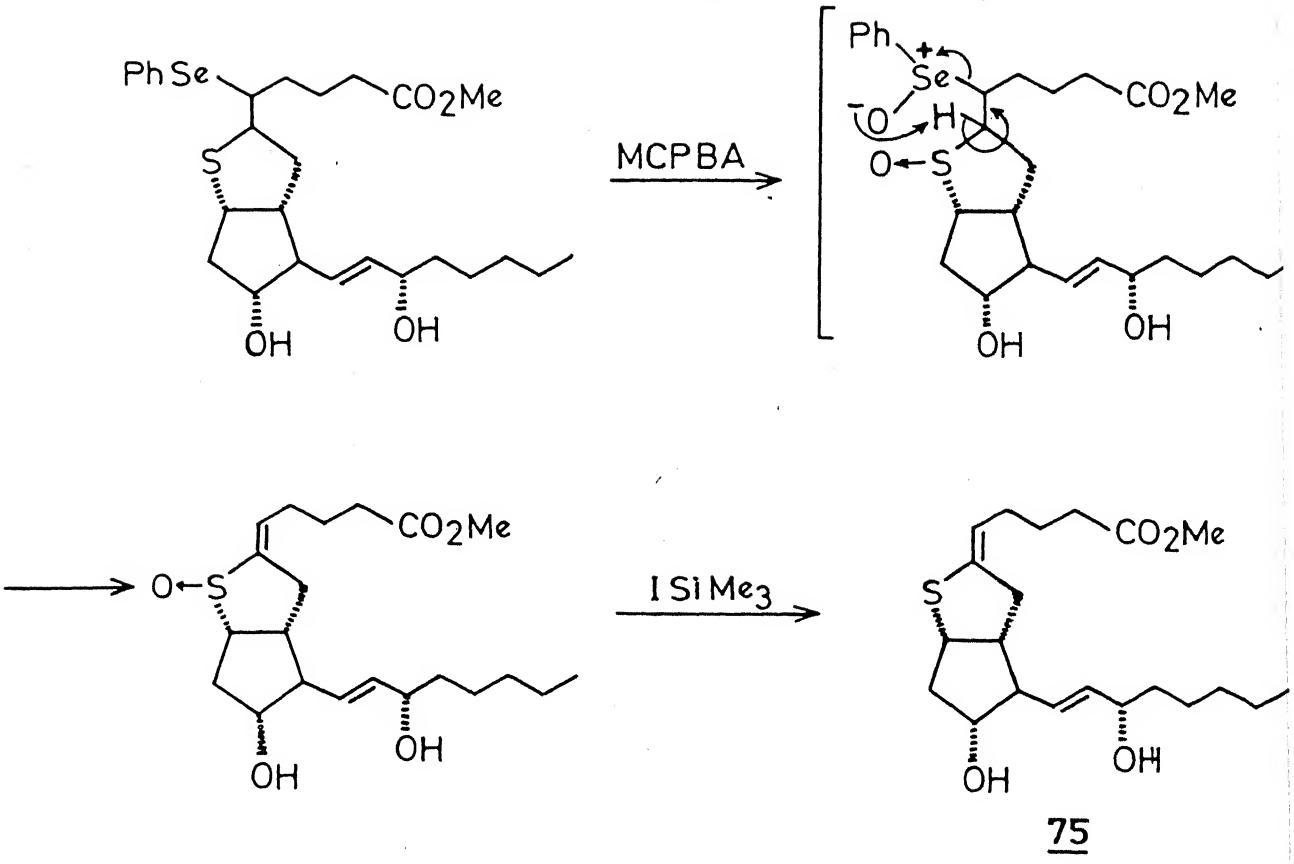
II.A.3 Reduction of Sulphoxides to Sulphides

II.A.3(i) Background

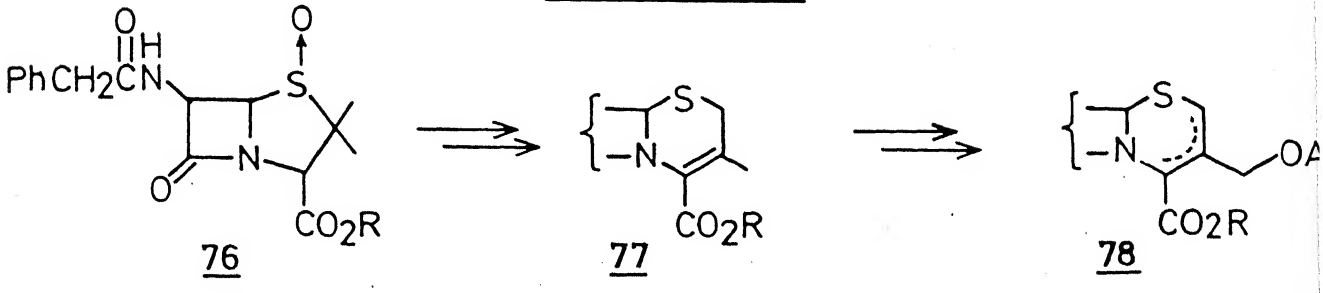
Chemistry of sulphur compounds has received considerable attention in recent years. Formation of sulphoxides activates the α-carbon of the substrate and as result of which a number of regioselective transformations could be carried out at the α-position. In all these cases, thereafter, deoxygenation of the sulphoxide becomes essential. For example, Nicolaou et al.[1] have recently reported a synthesis of thiaprostaglandin 75 , in which formation of sulphoxide and selenoxide followed by the elimination of selenoxide to produce a double bond was the key step. Due to the presence of this sulphoxide, the double bond was regioselectively formed. Later, the deoxygenation of the sulphoxide with iodotrimethylsilane was performed to complete the synthesis (Scheme II.21).

In a similar fashion, in the chemistry of penicillin and cephalosporin type of compounds, the formation of sulphoxide was useful for some selective transformations and therefore the deoxygenation became equally important.[2] Thus, compound 76 was converted into 77 through a series of steps. Further transformation of 77 into 78 led to a mixture of two olefins which were difficult to separate. Formation of their sulphoxides followed by regioselective isomerization of the double bond led to the formation of a single compound 79, which was then deoxygenated to the required biologically active pinem 80, using phosphorus pentasulphide (P_2S_5) (Scheme II.22).[2,3] Due to the importance

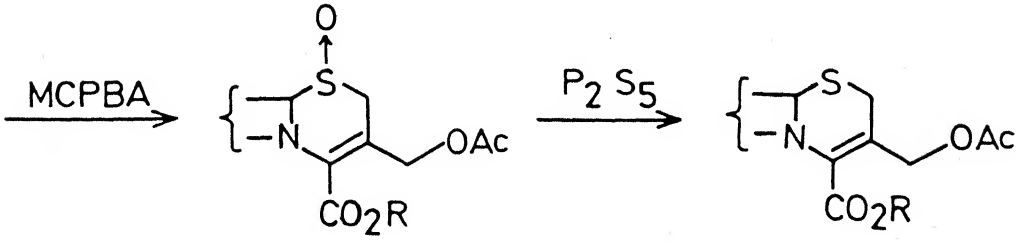


75

SCHEME II·21



76 77 78

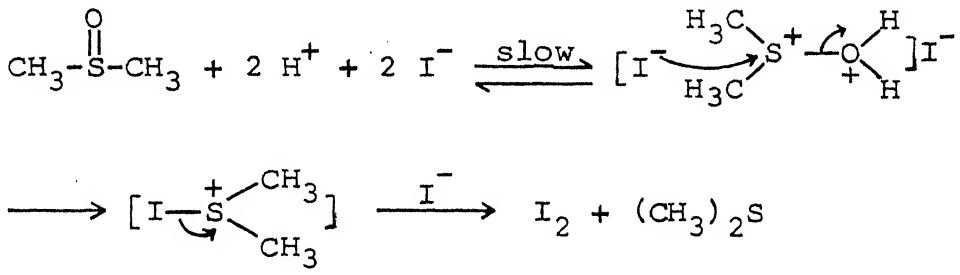


79 80

SCHEME II·22

of such transformations involving sulphoxides, their deoxygenation has become very important and literature survey indicates that a plethora of reagents[4] have been developed for this purpose.

Classically, the reduction of sulphoxides was carried out by using zinc-acetic acid,[5] or with hydrogen iodide.[6] The latter reaction was shown to involve a doubly protonated species, as shown in Scheme II.23.



SCHEME II.23

The reduction is clean and stoichiometric and therefore has often been used as a convenient method for the determination of simple sulphoxides.

Hydride transfer reagents like lithium aluminium hydride and sodium borohydride-cobalt(III) chloride[7] systems, can reduce sulphoxides to sulphides. Trichlorosilane[8] reduces aromatic sulphoxides to the corresponding sulphides, while aliphatic sulphoxides give predominantly mercaptals.

Catalytic reduction of sulphoxides, by molecular hydrogen with rhodium(III) complexes[9] is known. Iron carbonyl $Fe(CO)_5$, also reduces both alkyl and aryl sulphoxides into sulphides[10]

via initial formation of complexes of the type, $R_2SO[Fe(CO)_3]$ or $[(R_2SO)_6][Fe(CO)_3]$.

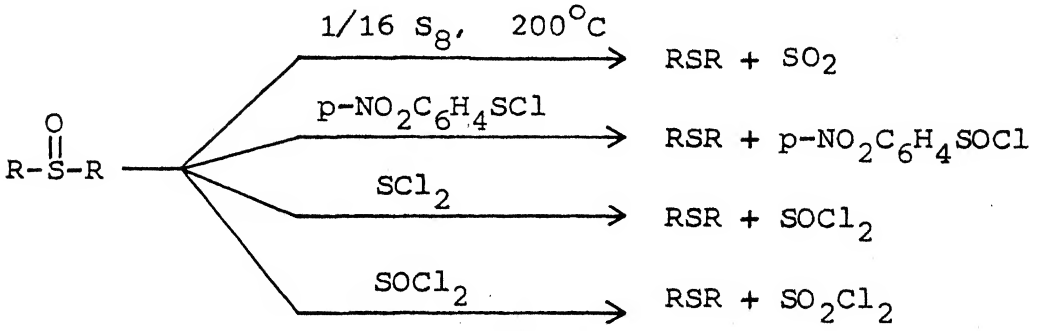
Sulphoxides are readily reduced to sulphides by treatment with thiols,[11] which in turn are oxidised to disulphides (Scheme II.24).

$$R_2SO + R'SH \underset{\text{slow}}{\rightleftharpoons} [R_2S(OH)(SR')] \xrightarrow{R'SH} R'SSR' + R_2S + H_2O$$

SCHEME II.24

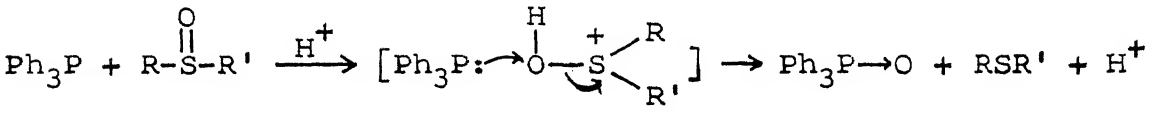
Use of a tertiary amine such as tributylamine, increases the yield. This reaction is useful for the "sweetening" of fuels in petroleum refining[12] and also for the oxidation of biologically active compounds such as a thiamine like molecule.[13]

Reduction of sulphoxides by oxygen transfer to sulphur electrophiles like arenesulphenyl chloride, sulphur dichloride and thionyl chloride are also known in the literature.[14] Simple heating of sulphoxides with elemental sulphur at high temperatures gives the corresponding sulphide with liberation of sulphur dioxide[14] (Scheme II.25).



SCHEME II.25

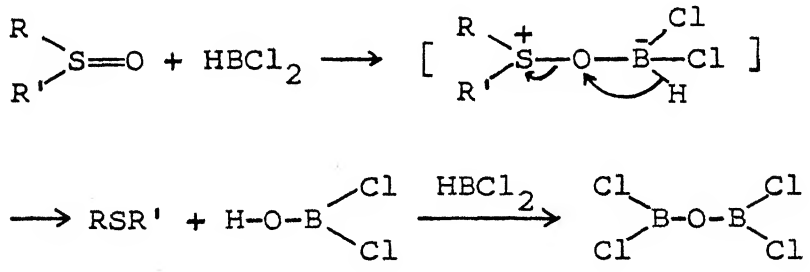
Transfer of oxygen to phosphorus compounds is also reported in literature. Reduction of sulphoxides by triphenylphosphine[15] has been shown to be acid catalysed and proceeds via nucleophilic attack of phosphorus centre on an acid complexed sulphoxide (Scheme II.26).



SCHEME II.26

Some of the earlier reactions, described above, require either elevated temperatures or the use of strong acids. In the recent past several new reagents like boron, phosphorus halides and some low-valent metal halides have been used to reduce sulphoxides to sulphides under milder conditions.

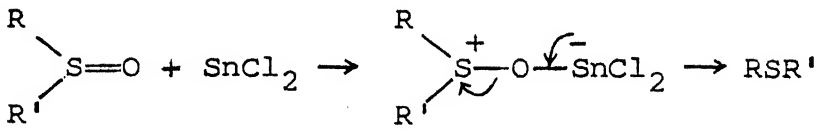
Brown and Ravindran[16] have demonstrated that dichloroborane reduces sulphoxides to sulphides (Scheme II.27). Excess of reagent does not reduce esters, ketones, amides and double bonds.



R = aryl or alkyl

SCHEME II.27

Ho et al.[17] have shown that Stannous chloride in the presence of conc. HCl is also capable of reducing sulphoxides to sulphides (Scheme II.28).



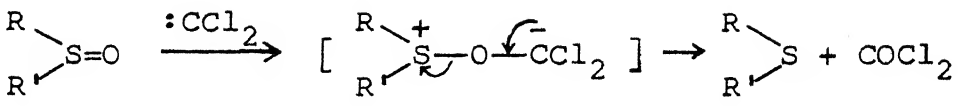
SCHEME II.28

Similarly, other low-valent metal halides, which are good Lewis acids and have good affinity for oxygen, have successfully been demonstrated to reduce sulphoxides to sulphides. Thus the low-valent titanium Ti(II)[18] generated from titanium(IV chloride with either $NaBH_4$ or zinc dust, reduces sulphoxides neatly to sulphides. Chromium(II) chloride[19] also reduces sulphoxides to sulphides albeit in low yields. These reagents are not chemoselective, as they are known to reduce other oxygen containing functional groups like aldehydes, ketones and nitro compounds. Other transition metals in their low-valent state, like molybdenum(III) and vanadium(II) are also capable of reducing sulphoxides to sulphides.

Phosphorus halides (PCl_5 and $POCl_3$) are known to give Pummerer rearrangement products with sulphoxides. However, in the presence of enamines or N,N-dimethylaniline (DMA),[20] reduction of sulphoxides to sulphides takes place.

The electron deficient dichlorocarbene has been shown to deoxygenate sulphoxides to sulphides under phase transfer

catalytic conditions,[21] via a zwitterionic intermediate (81) (Scheme II.29a):



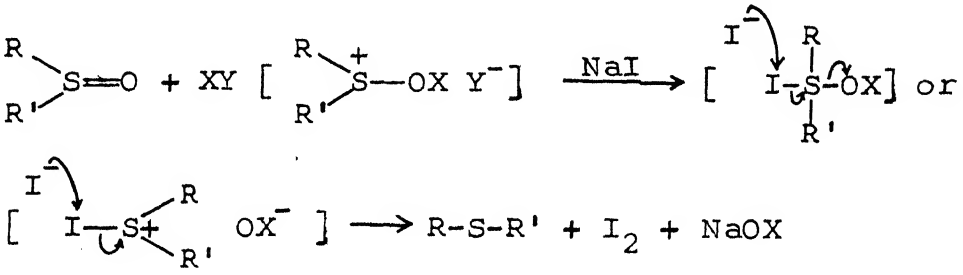
SCHEME II.29a

Benzylic and allylic sulphoxides, however, led to complications.

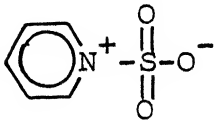
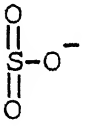
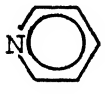
Olah et al.[22] have developed several silicon based reagents for the deoxygenation of sulphoxides and some of these methods have been used in the synthesis of complex molecules by other workers.[1] They have shown that bromotrimethylsilane, iodotrimethylsilane and phenyltrimethylsilane are all capable of reducing sulphoxides to sulphides. However, the former two reagents with dibenzyl sulphoxide lead to a mixture of products.

Recently, several novel reagent systems, having a combination of an electrophilic reagent and iodide ion have been shown to be highly efficient and attractive for the conversion of sulphoxides to sulphides. The electrophilic centre (either Si, P, C or even S atom) of the reagent, being a hard acid combines with the sulphoxide oxygen, a hard base, and forms a sulphonium complex 82 . The iodide ion being a soft base then attacks the sulphur atom (a soft acid) and its polarity is now reversed. A second iodide ion then further attacks the positive

polarised iodide of species 83, forming iodine and the corresponding sulphide (Scheme II.29b). The electrophilic reagents used in combination with iodide include, trifluoroacetic anhydride,[23] oxalyl chloride,[24] triphenylphosphonium iodide,[25] pyridine-sulphur trioxide complex,[26] chlorosulphonyl isocyanate,[2] iodotrimethylsilane (from chlorotrimethylsilane & sodium iodide) and most recently trichloromethylsilane.[29]



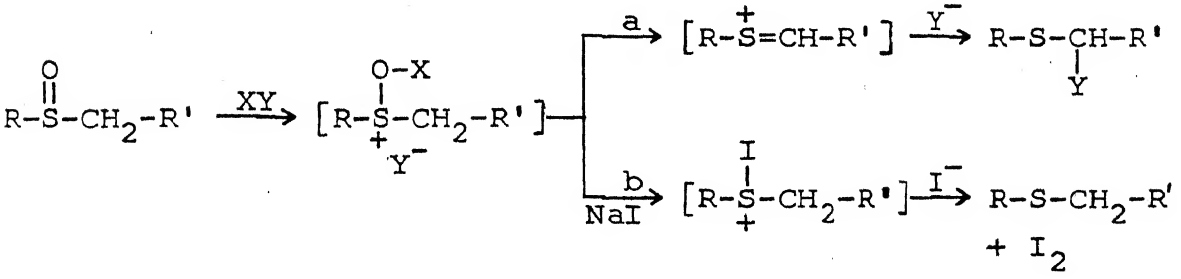
R,R' = aryl or alkyl

Reagent XY	X	Y
$(CF_3CO)_2O$	CF_3CO	CF_3COO^-
$(COCl)_2$	COCOCl	Cl^-
Ph_3P^+-I I^-	Ph_3P^+-I	I^-
		
$ClSO_2NCO$	$ClSO_2$-$\bar{N}$-C=O	-
$SiMe_3I$ ($SiMe_3Cl$+NaI)	$SiMe_3$	I^-
$SiMeCl_3$	$SiMeCl_2$	Cl^-

SCHEME II.29b

II.A.3(ii) Present Work

For the reduction of sulphoxides to sulphides a large number of reagents are reported in the literature, as presented in the background part of this section. A combination of sodium iodide and an electrophile (XY), as mentioned towards the end of the background, (Scheme II.30, vide infra) seem to be preferred reagent system for such reductions. With other reagents such as HI, Ph_3P, $Fe(CO)_5$ higher temperatures are required for the reduction to occur. Also, on the other hand, in case of chlorinated electrophiles such as Ph_3P/CCl_4, PCl_5, $SOCl_2$ and $:CCl_2$, Pummerer rearrangement products were mainly obtained from sulphoxides bearing active α-hydrogens (Scheme II.30, path a).[30] Further, with iodotrimethylsilane and bromotrimethylsilane, no clean reaction was found in case of dibenzyl sulphoxides.[22] In cases, where an electrophile-NaI combination[23-29] is used,

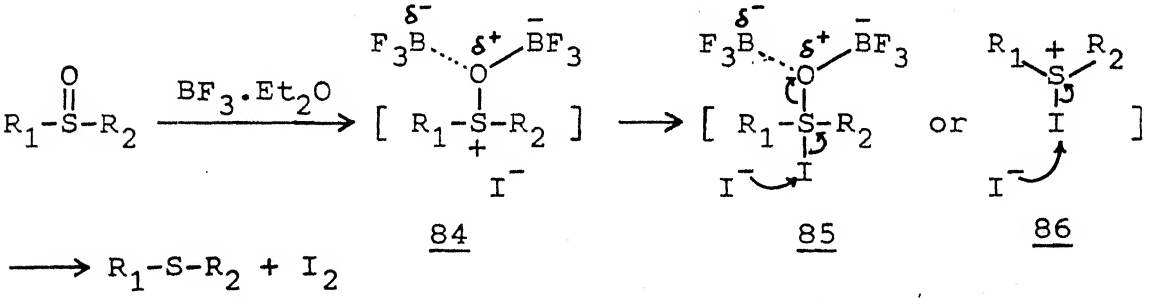


SCHEME II.30

generally low temperatures are needed and no Pummerer rearrangement takes place. The use of excess NaI is responsible for avoiding Pummerer rearrangement (Scheme II.30, path b).

The choice of a typical electrophile for the reduction depends upon the system to be used. Furthermore, for large scale reduction, a cheaper and effective electrophile which is easily available would be welcomed. With this view in mind we undertook the present study, wherein we have demonstrated the combination of sodium iodide and boron trifluoride etherate to be an extremely effective system for the reduction of sulphoxides under mild conditions. It is expected, that the easy availability and cheaper cost of boron trifluoride etherate would make this a highly useful reagent system.

A plausible mechanism for the reduction is illustrated in Scheme II.31. The sulphoxide oxygen (a hard base) complexes with



SCHEME II.31

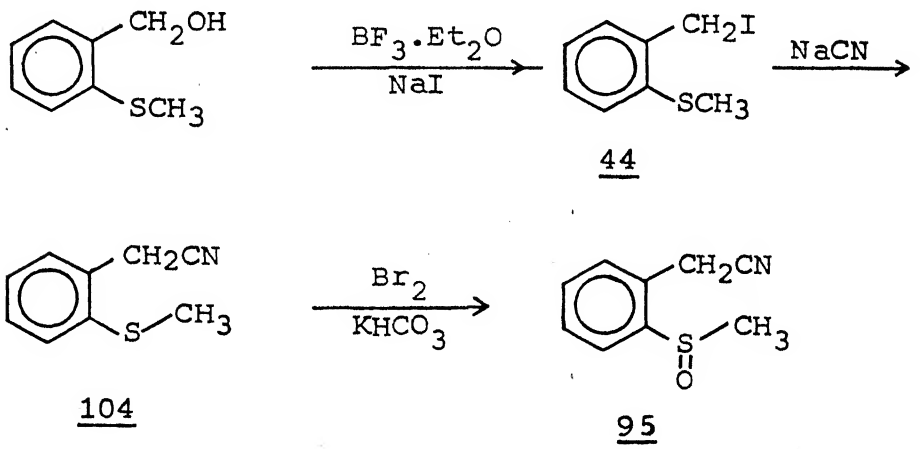
the hard Lewis acid i.e. BF_3, and the soft base I^- attacks the positively charged sulphur (a soft acid), followed by concomitant formation of iodine and deoxygenation. The excess $BF_3.Et_2O$

present in the reaction medium possibly assists deoxygenation (structures 84 & 85). It is possible that the intermediate 84 may lead to 86 without going to the other intermediate 85. Both 85 and 86 decompose to the sulphide with liberate of iodine.

Various sulphoxides chosen for this study are listed in Table II.3. The sulphoxides were neatly reduced to sulphides in yields ranging from 90-98% and in as short times as 20 min. to 5 hr. Diaryl, aryl-aliphatic and aliphatic sulphoxides were all reduced neatly to sulphides. Functional groups such as ester in 94, methoxy in 93, and cyano in 95 were unaffected under the reaction conditions. Diaryl sulphoxides 91 and 92 required longer reaction times (5 hr) for the reduction to be complete, as in the case of other reagent systems. This could be attributed to the fact that the sulphonium intermediate 84 in these cases is highly stabilized by resonance with the aryl ring, thereby getting deactivated for the attack of the I^- ion. In case of dibenzyl sulphoxide (90) and α-phenylsulphinyl methyl acetate (94) no Pummerer rearrangement products were obtained. This could be attributed to the fact that the intermediate 84, instead of losing an α-proton, is preferentially attacked by the iodide ion (present in large excess) on sulphur atom, which eventually leads to the formation reduced product.

Sulphones were found to be inert towards this reagent system. Thus, diphenyl sulphone was recovered completely even after prolonged refluxing with $NaI-BF_3.Et_2O$.

All the sulphoxides (87-94) and the corresponding sulphides (96-103), except (o-cyanomethyl)phenyl methyl sulphoxide 95 and the corresponding sulphide 104 are known in literature. 105 was prepared by the action of NaCN on (o-iodomethyl)phenyl methyl sulphide 44 which in turn was prepared by the procedure developed by us which is mentioned in the Section II.A.1(ii) (Scheme II.32). The sulphide 104 was then oxidized with Br_2-$KHCO_3$ to give sulphoxide 95 (yield, 90%, m.p. 175°C).



44

104

95

SCHEME II.32

II.A.3(iii) Experimental

The details of the instruments used are the same as mentioned in Section II.A.1(iii). Also the reagents and solvents were purified as described in the same section.

Starting Materials

Diphenyl sulphoxide(91) and di-p-chlorophenyl sulphoxide 92 were prepared by Friedel-Crafts reaction[31] using thionyl chloride. All the other sulphoxides used for reductions were prepared by the oxidation of the corresponding sulphides with $Br_2/KHCO_3$[32] reagent in two phase system,or by using sodium metaperiodate.[33]

General Procedure for the Oxidation of Sulphides to Sulphoxides:

(a) By $Br_2/KHCO_3$ reagent in a two phase system

To a solution of 10 mmol sulphide in 20 ml dichloromethane was added 20 ml of 10% aq. $KHCO_3$ solution and the reaction flask immersed in a cold water bath (15-20°C). A solution of Br_2 (10 mmol) in 5 ml dichloromethane was slowly introduced with vigorous stirring of the reaction mixture. The colour of Br_2 disappeared quickly and the formation of sulphoxide was monitored by tlc. After the reaction was completed the organic layer was separated, the aqueous layer saturated with sodium chloride and extracted with dichloromethane. The combined organic layers were dried

over anhyd. Na_2SO_4, the solvent was evaporated, and the crude product distilled (or recrystallized) to give pure sulphoxide. Thioanisole sulphoxide (87), (p-methyl)thioanisole sulphoxide (88) and (o-cyanomethyl)thioanisole sulphoxide (95) were prepared from the corresponding sulphides by this method.

(b) By sodium metaperiodate

To a stirred solution of 10 mmol sulphide in 45 ml of water methanol mixture (1:1) was added 11 mmol of $NaIO_4$ and the stirring continued at $0^{\circ}C$ for 8-10 hr. The reaction mixture was then extracted with chloroform (3 x 20 ml), washed with H_2O, brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave the crude sulphoxide which was then recrystallized (or distilled).

Dibenzyl sulphoxide 90, benzyl phenyl-sulphoxide 89, m-methoxythioanisole sulphoxide 93 and α-phenylsulphinyl methyl acetate 94 were prepared by this method.

Preparation of (o-Cyanomethyl)thioanisole Sulphoxide (95)

To (o-iodomethyl)thioanisole (cf. compound 44, Sec. II.A.1(iii))(3.17 g, 12 mmol) in 10 ml acetone was added 0.647 g (13.2 mmol) of sodium cyanide and refluxed it for 4 hrs. The acetone was removed by distillation and the residue extracted into ether (20 ml). The ether layer was washed with water brine and dried over anhyd. Na_2SO_4. The crude product obtained after evaporation of solvent was purified by column chromatography (silica gel) with benzene as eluent. The product obtained was then

recrystallized from ethanol to give (o-cyanomethyl)thioanisole 105 as colourless crystals (yield: 1.7 g; 87%), m.p. 35°C.

IR ($CHCl_3$), ν_{max} (cm^{-1}): 2260 ($\nu_{C\equiv N}$).

1.63 g (10 mmol) of this compound was oxidized by the Br_2/$KHCO_3$ method. Recrystallization of the product from $CHCl_3$-Hexane gave the sulphoxide 95 as colourless needles (yield: 1.6 g; 90%), m.p. 175°C.

IR (KBr), ν_{max} (cm^{-1}): 2260 ($\nu_{C\equiv N}$).

PMR ($CDCl_3$), δ (ppm): 2.84 (s, 3H, S(O)CH_3), 3.96 (s, 2H, CH_2CN), 7.2-8.17 (m, 4H, aromatic).

Mass spectrum, m/e (rel. ab.): 179 (31, M^+), 164 (38, M^+-CH_3), 137 (100), 136 (42), 109 (63), 89 (33), 63 (30).

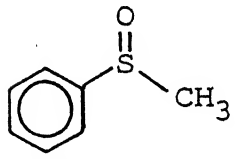
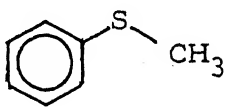
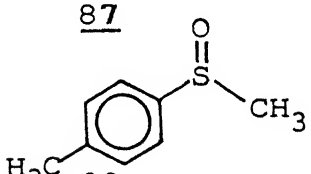
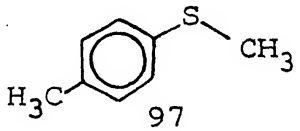
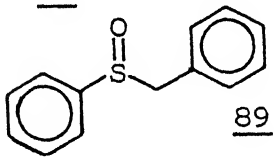
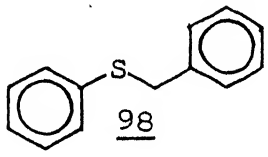
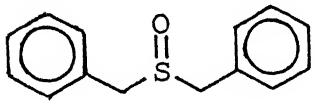
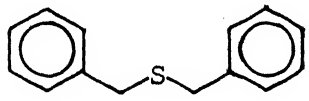
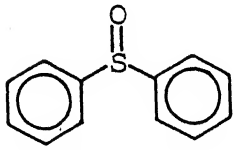
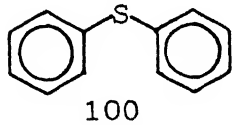
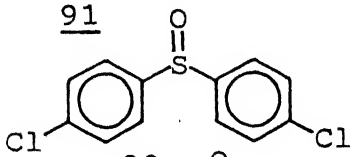
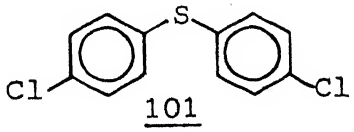
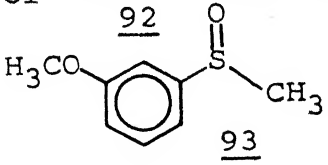
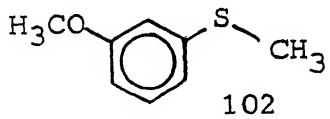
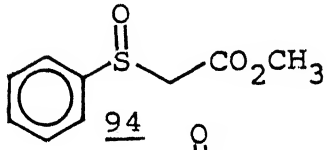
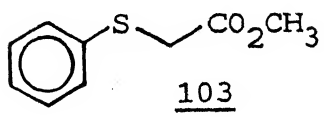
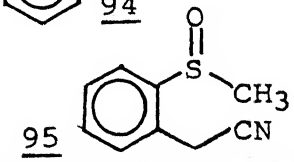
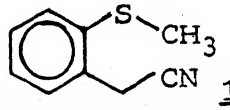
General Procedure for the Reduction of Sulphoxides to Sulphides Using NaI-$BF_3.Et_2O$

To a stirred solution of a sulphoxide (2.5 mmol) and sodium iodide (7.5 mmol) in 8 ml dry acetonitrile at 0°C was added a solution of freshly distilled $BF_3.Et_2O$ (7.5 mmol) in 2 ml acetonitrile during 10 mins. The reaction mixture was then brought to room temperature (wherever necessary) and stirred for a period as indicated in Table II.3. The reaction mixture was then poured into ice cold water (20 ml) and treated with 10% aq. sodium thiosulphate solution to decolourize the iodine liberated in the reaction, and then extracted with ether (3 x 15 ml). The combined

ether extracts were washed once with water and brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave pure sulphide which was further purified by distillation or recrystallization. All the sulphides thus obtained were identified by comparing their physical (m.p./b.p., tlc) and spectral (IR) characteristics with those of the authentic samples.

The yields, m.p./b.p. of the sulphides obtained by reduction are summarized in Table II.3.

Table II.3. Reduction of Sulphoxides to Sulphides

Sulphoxide	Sulphide	Time (min)	Yield (%)	m.p.* or b.p./torr (°C) (lit.value)
 87	 96	40	90	87/15 (188)[34]
 88	 97	40	90	94/15 (96-100/18)[35]
 89	 98	40	98	41* (41-43)[34]
 90	 99	20	96	49* (49)[34]
 91	 100	300	96	100/1.0 (189/50)[34]
 92	 101	300	98	96* (98)[34]
 93	 102	60	90	130/15 (126/16)[36]
 94	 103	120	95	133/10 (262-3)[34]
 95	 104	90	95	35*

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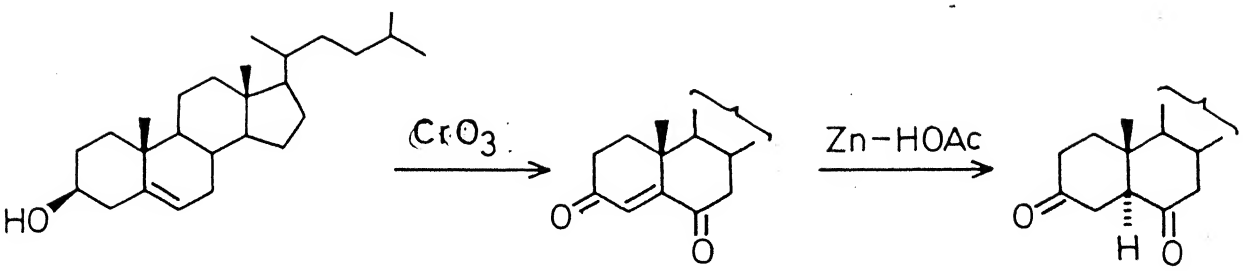
II.A.4 Reduction of Conjugated Ene-Diones

II.A.4(i) Background

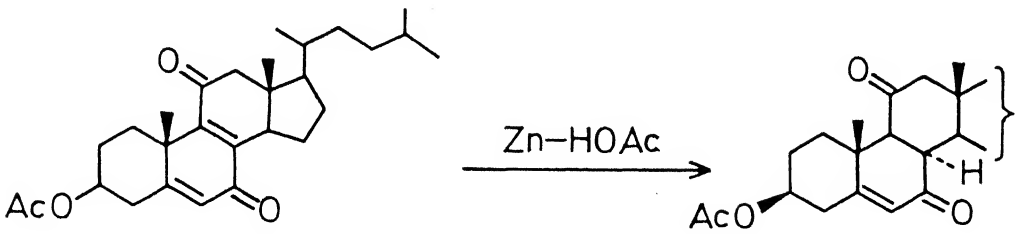
The reduction of the double bond in conjugated ene-diones provides a convenient method for the synthesis of 1,4-diketones. Because of the easy accessibility of ene-diones in the steroidal systems, the synthetic utility of their reduction to 1,4-diketones was first recognized in steroid chemistry.[1] For example, cholesterol (105) was readily oxidized to Δ^4-cholestene-3,6-dione (106) which upon reduction with zinc-acetic acid provided the 1,4-diketone 107 (Scheme II.33). Similarly, the ene-dione 108 was reduced with zinc-acetic acid to the dione 109.[2] Both the 1,4-diketones 107 & 109 have been utilized for further synthetic transformations.

Similarly, in the synthesis of cycloartenol (113), one of the important transformations involved the conversion of ene-dione 111 into the 1,4-diketone 112 (which was obtained by CrO_3 oxidation of 110) by reduction with zinc-acetic acid (Scheme II.34). The 1,4-diketone 112 was further converted through a number of steps into cycloartenol(113).[3]

A survey of literature indicates that besides zinc-acetic acid (vide supra),[4] four other reducing systems have been successfully utilized to bring about the reduction of conjugated ene-diones.

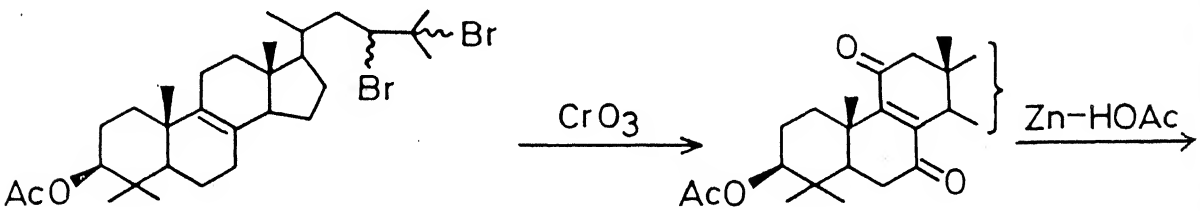


105 106 107

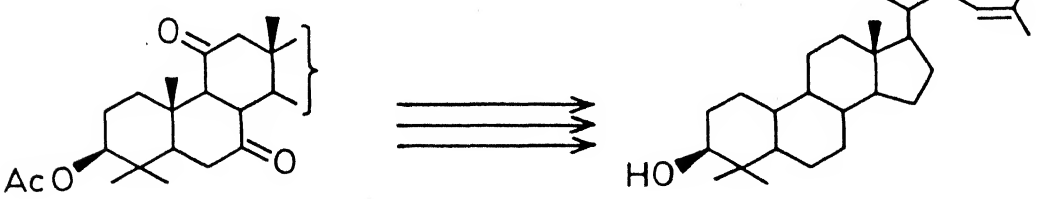


108 109

SCHEME II·33



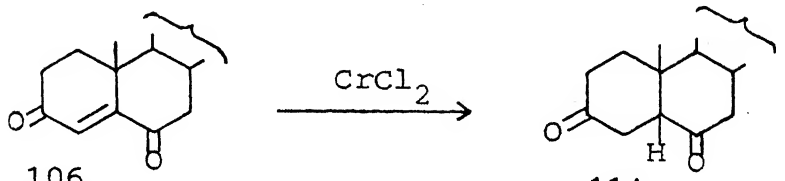
110 111



112 113

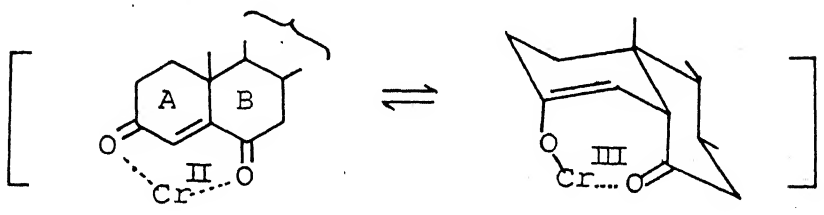
SCHEME II·34

Chromium(II) chloride has been shown by Hanson and Premuzic[5] to be an efficient reducing agent for reduction of ene-diones. For example, cholest-4-ene-3,6-dione (106) was reduced by Cr(II) chloride to the 1,4-dione 114 (Eqn. II.16).



106 114 ..(II.16)

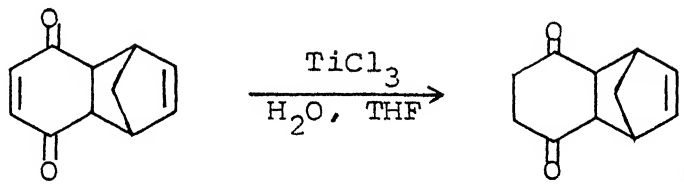
Interestingly, the product 114, obtained in this case, was the 5β-isomer, unlike reduction with zinc-acetic acid, where 5α-isomer 107 was obtained (cf. Scheme II.33). This was rationalized by visualizing a chelate complex formation between the chromium(II) ion and the two carbonyl functions in the transition state, where A & B rings assume a favourable cis-fusion.[6]



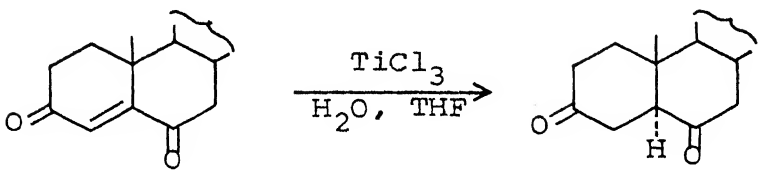
Some other steroidal ene-diones were shown to be reduced by Cr(II) chloride, and in all the cases examined the preference for β-stereochemistry was observed. However, the yields in these reactions were not very impressive and certain substrates were found to be resistant towards reduction.

McMurry and Blaszczak[7] in 1974 have reported a fairly simple and general reduction procedure for conjugated ene-diones utilizing low-valent titanium reagent. A variety of

substrates were reduced by aqueous titanous chloride. Two typical examples are shown in Eqns. II.17 & II.18. However,



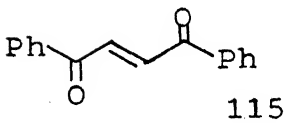
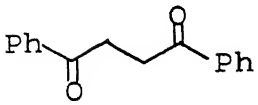
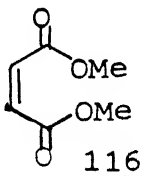
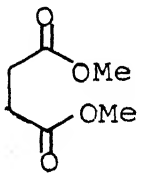
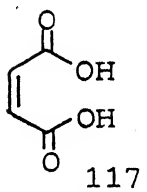
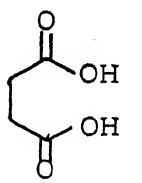
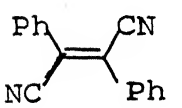
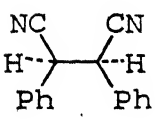
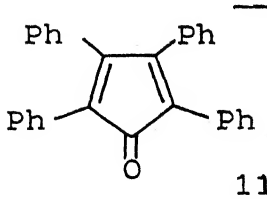
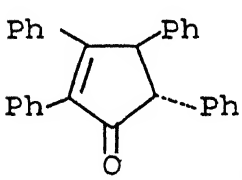
..(II.17)



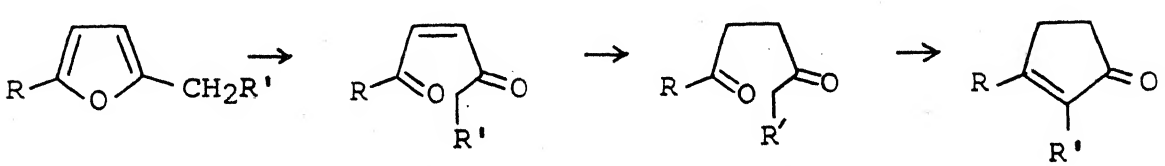
..(II.18)

ene-diesters (diethyl maleate) were resistant to reduction, while ene-dicarboxylic acids (maleic acid) gave poor yields of the saturated dicarboxylic acid.

Subsequently Toda and Iida[8] in 1976 reported that zinc-zinc chloride ($Zn-ZnCl_2$) is superior to zinc-acetic acid as a reducing agent, since reductions with this system could be performed under milder conditions in high yields. Double bonds placed between two cyano groups, esters groups and carboxylic acids were reduced neatly, giving high yields of the saturated products. Even simple enones were reduced with $Zn-ZnCl_2$ system. Some typical substrates (115-119), which were reduced with $Zn-ZnCl_2$ system to the corresponding 1,4-di-ketones 120-124 are listed below:

Substrate	Product	Yield (%)
 115	 120	83
 116	 121	95
 117	 122	94
 118	 123	71
 119	 124	71

Importance of 1,4-diketones as valuable intermediates in the synthesis of natural products having cyclopentenoid ring systems, is well recognised.[9] One of the convenient methods[10] to produce such compounds, involves conversion of furan derivatives to ene-dicarbonyl compounds followed by reduction of the double bond (Scheme II.35). From this point



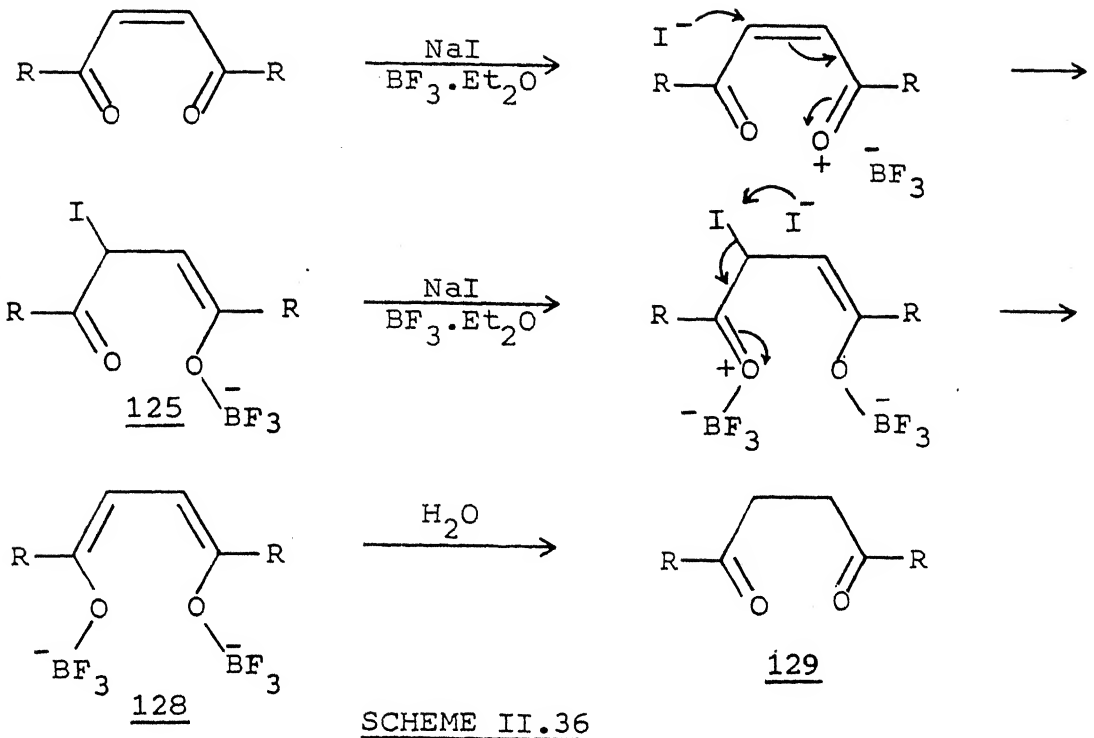
SCHEME II.35

of view, Piancatelli et al.[11] have developed a simple reagent system viz., NaI and conc. HCl which was found to reduce ene-dicarbonyl compounds to 1,4-diketones in almost quantitative yields. For example, Δ^4-cholestene-3,6-dione (106) was reduced to the 5α-3,6-dione 107 in 100% yield using NaI:HCl in 4:4 molar equivalents of the substrate. But with certain substrates large excess of the reagents were required, although the reduction was quantitative. Double bond flanked by carboxylic acid groups and esters were not reduced by this reagent system.

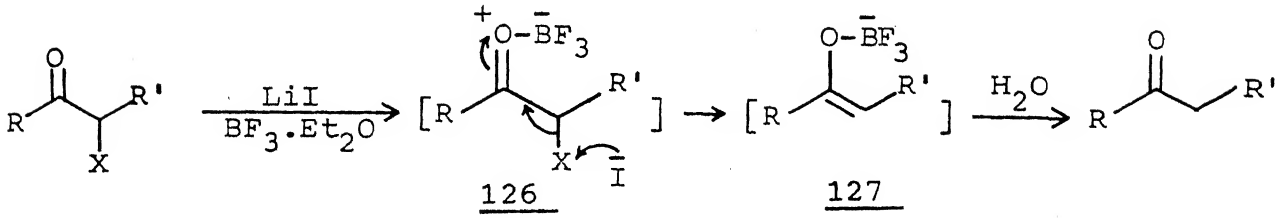
II.A.4(ii) Present Work

Importance of conversion of conjugated ene-diones to 1,4-diketones, which in turn could be easily transformed into cyclopentane ring systems,[9] has been highlighted in the background part of this section. The literature work concerning the reduction indicates clearly that NaI-HCl reagent system, developed by Piancatelli et al.,[10] seems to be a high yielding and cheap method for such a reaction. However, these conditions, where conc. HCl is used in large amounts are highly acidic and hence development of a method(s) under relatively neutral conditions is required. With this view in mind, and also the fact that NaI-BF_3.Et_2O has resulted into an extremely mild reagent system for various transformations (as presented in the first three sections of this chapter), we undertook the present study. It was expected, on the basis of HSAB principle,[13] that an ene-dione would coordinate through oxygen, a hard base, with the hard acid i.e., BF_3, followed by attack of the soft nucleophile, i.e. I^- on the soft β-carbon resulting in the formation of an intermediate 125 (Scheme II.36). As it is known in the literature that α-haloketones are reduced to the corresponding ketones by means of LiI-BF_3.Et_2O [12] via intermediates 126 and 127 (Scheme II.37), it was therefore expected that the intermediate 125 derived from an ene-dione should yield another intermediate 128 in the presence of an excess of NaI-BF_3.Et_2O. This intermediate 128 would then

give the 1,4-diketone 129 upon aqueous treatment.



SCHEME II.36



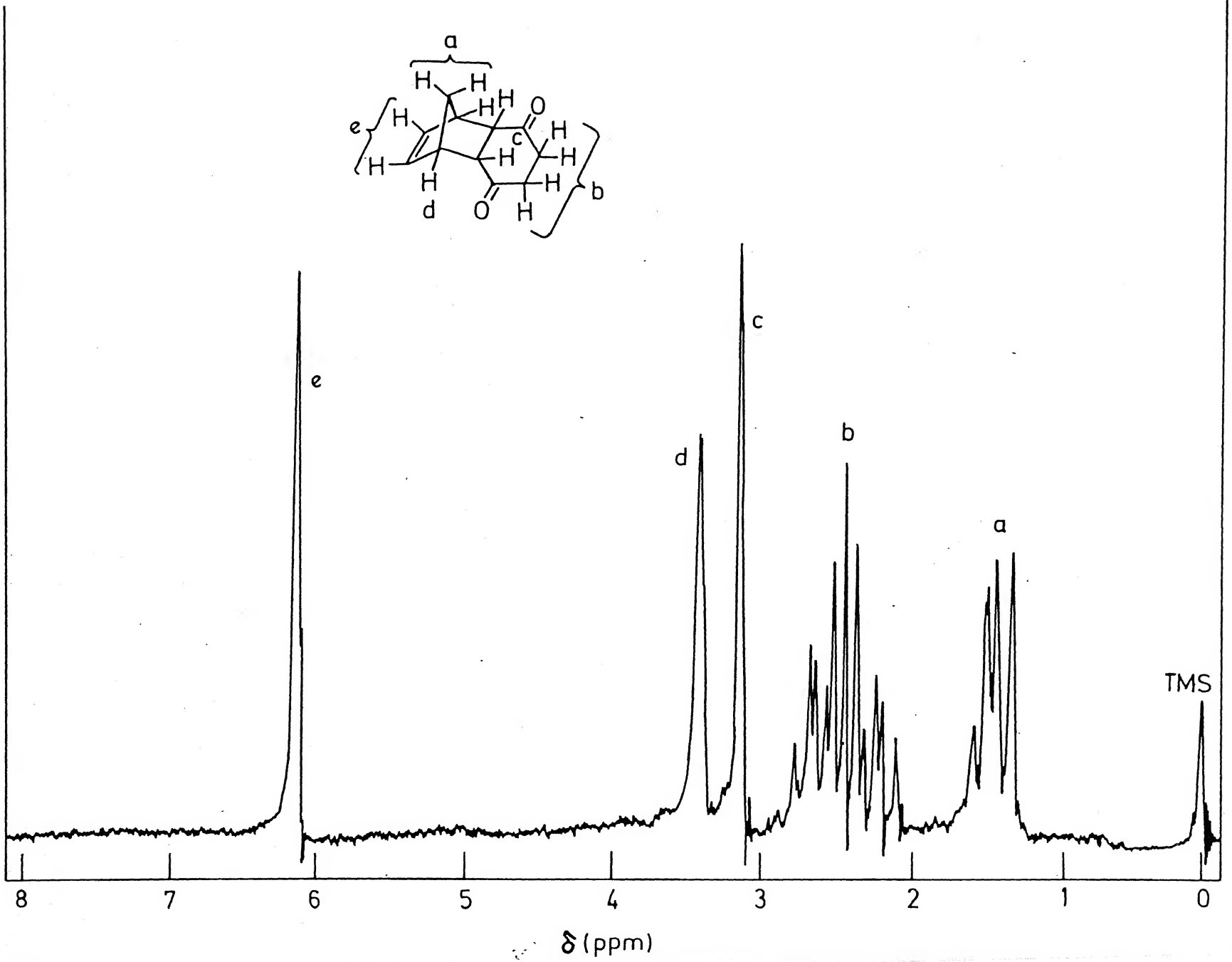
X = Cl, Br, I

SCHEME II.37

It was indeed found that a number of ene-diones (130-135) (Table II.4) could be converted into the corresponding reduced products 136-141, respectively in 88-99% yields. Thus, dibenzoylethylene (130) reacted with NaI-$BF_3.Et_2O$ (2.5 molar equiv. of each)

in 5 min. at 0°C to produce the dibenzoylethane 136 in 98% yields (m.p. 144°C, lit.[18] m.p. 145°C; IR (KBr): $\nu_{C=O}$ at 1675 cm^{-1}). In a similar fashion, benzoquinone (131) gave hydroquinone (137) in 99% yield (m.p. 172°C, lit.[19] m.p. 171°C) in 5 min. at 0°C and naphthaquinone (132) gave 1,4-dihydroxynaphthalene 138 (m.p. 176°C, lit.[19] m.p. 176°C) in 88% yield with NaI:$BF_3.Et_2O$ 2.5:3 molar equiv. at 0°C for 10 min. followed by 20 min. at room temperature. The ene-dione 133 was prepared according to literature procedure,[17] by reacting benzoquinone with cyclopentadiene, whose IR spectrum showed a strong absorption at 1660 cm^{-1} characteristic of an α,β-unsaturated carbonyl group. When 133 was treated with NaI-$BF_3.Et_2O$ (2.5 molar equiv. of each) at 0°C for 10 min. 98% yield of the corresponding reduced product 139 was obtained, The IR spectrum showed absorption at 1700 cm^{-1} ($\nu_{C=O}$) indicating the absence of conjugation with the carbonyl groups. Its ^1H NMR spectrum showed absorptions at δ 1.17 - 1.60 (m, 1H, CH_2 bridge), 1.01 - 2.90 (m, 5H, $\underset{O}{\overset{\|}{C}}-\underline{CH_2}$'s and 1H of CH_2 bridge), 3.07 (d, 2H, methines α to $>C=O$), 3.40 (m, 2H, allylic) and 6.1 (m, 2H, olefinic). The spectral characteristics are in accordance with the structure of 139.

Δ^4-Cholestene-3,6-dione 134 (IR (KBr): $\nu_{C=O}$ at 1675 cm^{-1}) was prepared according to literature procedure[14] by oxidizing cholesterol with $Na_2Cr_2O_7$. The dione 134 reacted smoothly with $BF_3.Et_2O$-NaI (3 equiv. each) at 0°C for 5 min. and then at room temperature for 10 min. to yield 89% of the reduced product 5α-cholestan-3,6-dione (140), m.p. 171-172°C (lit.[15] m.p. 172°C).


a
H
H
H
H
O
e
H
c
H
H
H
H
H
H
H
b
d
O
H
e
c
d
b
a
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

Its IR spectrum (KBr) showed strong absorption at 1705 ($\nu_{C=O}$) cm^{-1}, indicating loss of conjugation of the carbonyl groups. Its ^1H NMR showed absence of olefinic protons.

Further, it was found that even ene-diester i.e., diethylmaleate 135 was reduced to diethylsuccinate 141 in 99% yield in 6 hr at room temperature.

Thus, the present procedure for the reduction of ene-diones using NaI-$BF_3.Et_2O$ is definitely much simpler and higher yielding compared to the ones where Zn/HOAc, Zn/$ZnCl_2$ and $CrCl_2$ have been employed. Although the present method is comparable to that by Pinacatelli[10] (where NaI-HCl has been used) in terms of reaction time and yields of the products, it certainly is less acidic and hence milder. Also, ene-diesters are reduced by NaI-$BF_3.Et_2O$ and hence advantageous compared to NaI-HCl which does not reduce ene-diesters.

II.A.4(iii) Experimental

The details regarding the instruments used, reagents and drying the solvents are the same as mentioned in Sec. II.A.1(iii).

Starting Materials

Dibenzoylethylene 130 was prepared by the known literature procedure by Friedel Crafts reaction[16] of fumaroyl chloride with benzene. Δ^4-Cholestene-3,6-dione 134[14] and the benzoquinone cyclopentadiene adduct 133[17] were also prepared by known procedures as described below.

Preparation of Δ^4-Cholestene-3,6-dione (134)

Cholesterol (2.0 g, 5 mmol) was dissolved in 18 ml of benzene by warming, and the solution was then cooled to 20°C. 18 ml of gl. acetic acid was then added to it and the mixture cooled to 15°C. A solution of $Na_2Cr_2O_7$ (prepared by dissolving 5.12 g of $Na_2Cr_2O_7$ in 18 ml acetic acid by warming and then cooling to 15°C) was added slowly to the cholesterol solution at 15°C and the mixture allowed to cool in a refrigerator for 48 hrs. The mixture was then extracted with petroleum ether (40-60°C) (3 x 10 ml) and the combined organic layers washed once with water. The organic layer was shaken with 10 ml of Claisen's alkali (prepared by dissolving 14 g KOH pellets in 10 ml distilled water, cooling to

room temperature adding 40 ml of methanol and again cooling), the lower layer was drawn off and charged with 20 ml of water, 50 g of ice, 16 ml of 30% HCl and 30 ml of ether. The organic layer was extracted the aqueous layer discarded. The ethereal layer was separated, washed with 10 ml of 5% Na_2CO_3, brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent and recrystallization of the residue from methanol gave 0.92 g (40% yield) of 134, m.p. 118-120°C (lit.[14] m.p. 124-125°C).

IR (KBr), ν_{max} (cm^{-1}): 1675 ($\nu_{C=O}$).

Preparation of the Adduct (133)

p-Benzoquinone (2.0 g, 18 mmol) was dissolved in 25 ml of absolute ethanol, cooled to about 10°C and 1.19 g (18 mmol) of cyclopentadiene was slowly added during 15 minutes. The reaction mixture was then stirred at room temperature for additional 30 mins. and then ethanol evaporated to give the crude product. Recrystallization of the residue from petroleum ether gave 133 (yield 50%), m.p. 72-73°C.

IR (KBr), ν_{max} (cm^{-1}): 1600 ($\nu_{C=C}$) and 1650 ($\nu_{C=O}$).

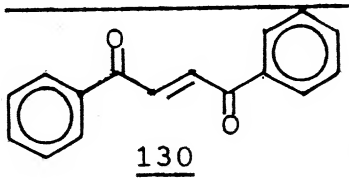
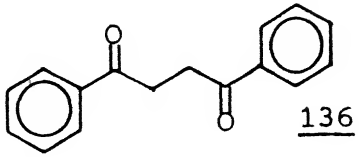
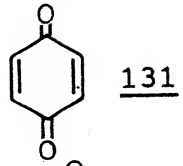
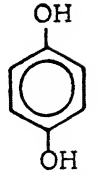
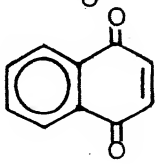
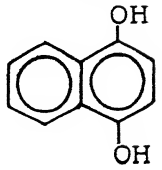
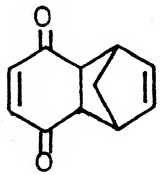
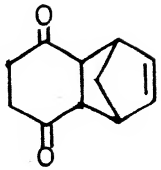
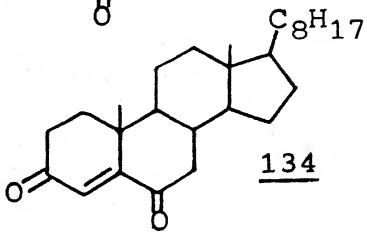
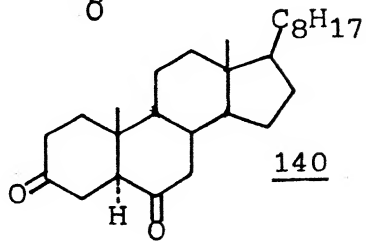
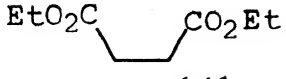
General Procedure for the Reduction of Ene-Diones with NaI-$BF_3.Et_2O$

To a stirred solution of the ene-dione (1.25 mmol) and sodium iodide (2.5-3.0 molar equiv. as in Table II.4) in 4 ml dry acetonitrile at 0°C (at room temperature in case of diethylmaleate 135 was added slowly $BF_3.Et_2O$ in 1.0 ml of acetonitrile. After the reaction was over (reaction and temperature are given in Table II.4

the reaction mixture was poured in 10 ml water and 10% aqueous sodium thiosulphate solution was added to decolourize the iodine liberated in the reaction. It was extracted with dichloromethane (3 x 10 ml) and the combined extracts were washed once with water, saturated brine, and then dried over anhyd. Na_2SO_4. Evaporation of the solvent gave the pure reduced products, which were further purified by distillation (or recrystallization). The yields, m.ps./b.ps. and IR spectral characteristics are summarized in Table II.4.

^{1}H NMR ($CDCl_3$) of 139, δ(ppm): 1.17-1.60 (m, 2H, $-CH_2-$ bridge), 1.01-2.90 (m, 4H, $-\overset{O}{\overset{\|}{C}}(CH_2)_2-\overset{O}{\overset{\|}{C}}-$), 3.07 (d, 2H, methines α to C=O), 3.40 (m, 2H, allylic), 6.10 (m, 2H, vinylic).

Table II. 4. Reduction of conjugated ene-diones with $NaI-BF_3.Et_2O$

Substrate	Product	$NaI-BF_3.Et_2O$ (molar eqvs.)	Reaction temp. °C	Reaction time (min)	Yield (%)	IR: ($\nu_{C=O}$) (cm^{-1})	m.p.* or b.p./torr (°C) (lit.value
 130	 136	2.5:2.5	0	5	98	1675	144* (145)[18]
 131	 137	2.5:2.5	0	5	99	-	172* (171)[18]
 132	 138	2.5:3.0	0 RT	10 20	88	-	176* (176)[18]
 133	 139	2.5:2.5	0	10	98	1695	a
 134	 140	3.0:3.0	0	5	89	1700	171* (172)[1a]
 135	 141	3.0:3.0	RT	6	99	1725	95/10 (218)[18]

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PART B: TRANSFORMATIONS UTILIZING ZINC-CHLOROTRIMETHYLSILANE REAGENT SYSTEM

Using zinc-chlorotrimethylsilane two different types of transformations have been carried out which are presented below.

II.B.1 Reduction of Epoxides to Alcohols

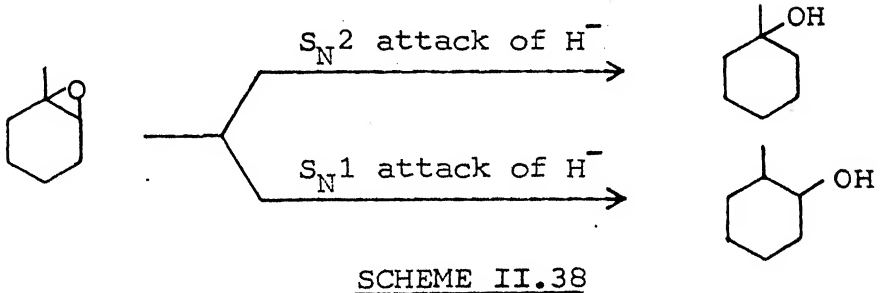
II.B.1(i) Background

Epoxides (or oxiranes) are versatile intermediates in organic synthesis.[1-4] The inherent polarity caused by the electronegative oxygen atom, and the strain of the three-membered ring, makes the epoxides susceptible to reaction with a large number of reagents viz., electrophiles, nucleophiles, reducing agents, and some oxidizing agents.[5]

Since epoxides can be easily prepared from olefins,[6,7] their reduction to alcohols provides an easy method for transforming olefins to alcohols in two steps. The reduction of epoxides to alcohols can be accomplished by a variety of reducing agents.[1,7] These reagents exhibit chemo, regio and stereoselectivity in varying degrees. The choice of the reagent depends on the nature of the substrate and the product desired. The methods for epoxide reduction that have been reported in literature could broadly be classified into three main categories: (a) those involving hydride transfer reagents, (b) metal-amine reductions and (c) catalytic hydrogenation.

(a) Hydride transfer reducing agents:

These are mainly aluminium or boron based reagents.[7,8] The regioselectivity of epoxide opening in unsymmetrical epoxides depends on whether S_N2 or S_N1 mechanism is operating. An S_N2 attack of hydride (H^-) would predominantly take place on the least hindered carbon and hence the ring cleavage would lead to the more substituted alcohol. On the other hand, when an S_N1 mechanism is operating, the epoxide oxygen atom first forms a complex with the electrophilic reagent,[9] thereby polarising the C-O bond in such a way that the positive charge is located on the more substituted carbon atom, which then becomes amenable to attack of H^- and hence the cleavage would result in the formation of a less substituted alcohol. Thus the nature of product/s is a function of the predominance of either S_N2 or S_N1 mechanism in these reactions (Scheme II.38).

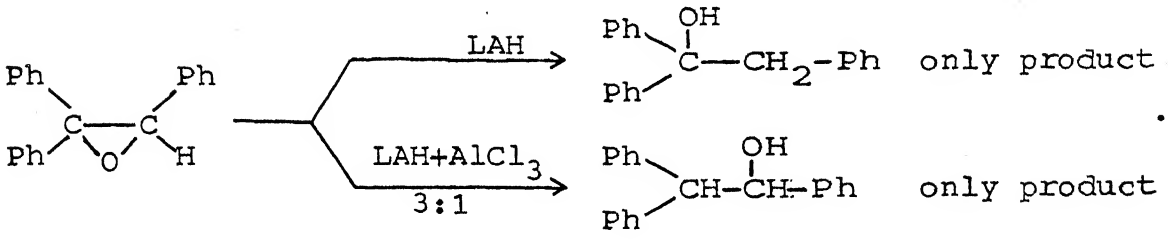


SCHEME II.38

The most common and extensively studied aluminium based hydride transfer reagent is the lithium aluminium hydride (LAH),[7,10] which reacts by an S_N2 mechanism giving predominantly a more substituted alcohol. With a combination of LAH and aluminium chloride[11,12] in the ratio 3:1, the direction of ring opening is, however, reversed and higher yields of less substituted

alcohols are obtained, presumably because the reactive species is now the electrophilic aluminium hydride (AlH_3) formed *in situ* from LAH and aluminium chloride (SchemeII.39):

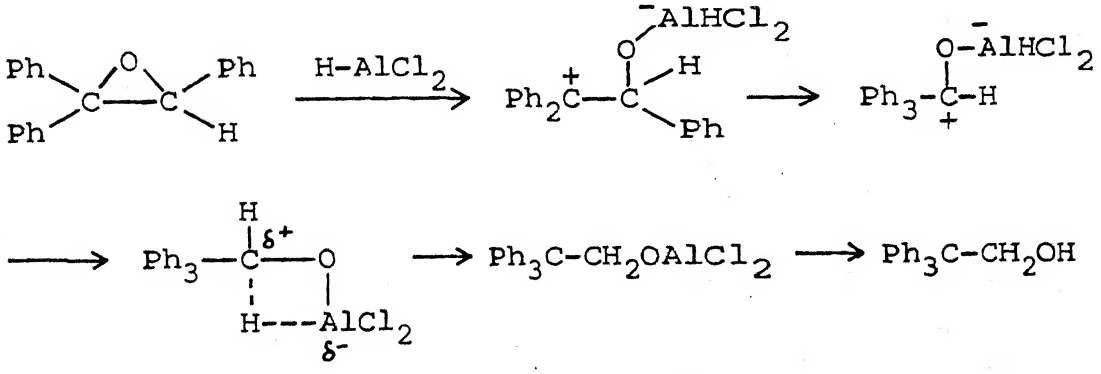
$$AlCl_3 + 3\ LiAlH_4 \longrightarrow 4\ AlH_3 + 3\ LiCl \qquad ..(II.1$$



..(II.2

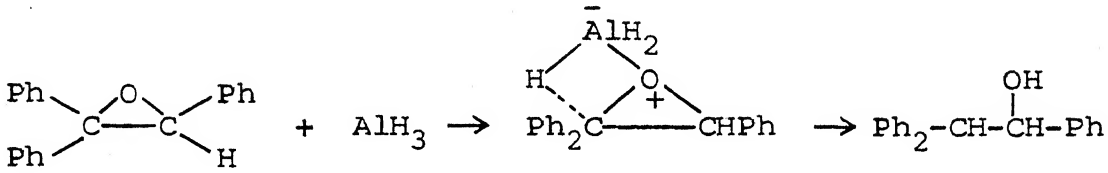
SCHEME II.39

Ashby and Prather[13] have determined the products of the reaction of LAH with $AlCl_3$ in stoichiometric ratios 3:1, 1:1, 1:3, and 1:4 and have shown that the products are AlH_3, H_2AlCl, $HAlCl_2$ and $HAlCl_2 + AlCl_3$, respectively. The first step in the reduction of an epoxide with these "mixed hydride" reagents involves complexation of the Al species at oxygen atom. If the Al species is a strong Lewis acid such as $HAlCl_2$ or $AlCl_3$, the ring opening to form a carbocation is rapid, followed by migration and reduction (Scheme II.40)



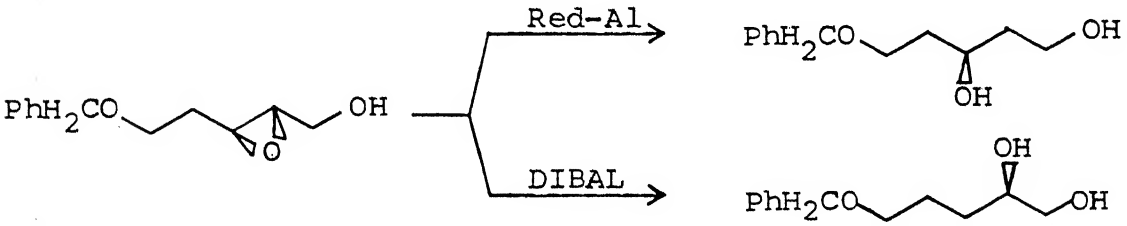
SCHEME II.40

However, if the Lewis acid is weak, such as AlH_3, the resulting complex is relatively stable and the reduction proceeds by a four-centered transition state to produce the expected alcohol (Scheme II.41):



SCHEME II.41

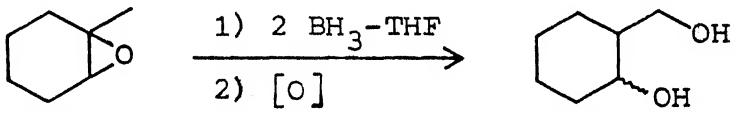
In a recent report Finan and Kishi[14] have demonstrated the remarkable complementary regioselectivities exhibited by the two hydride transfer reducing agents viz., Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] and DIBAL [diisobutyl aluminium hydride, $(i\text{-}Bu)_2AlH$]; towards allylic alcohol epoxides. While Red-Al gives a 1,3-diol, DIBAL gives mainly the 1,2-diol (Scheme II.42):



SCHEME II.42

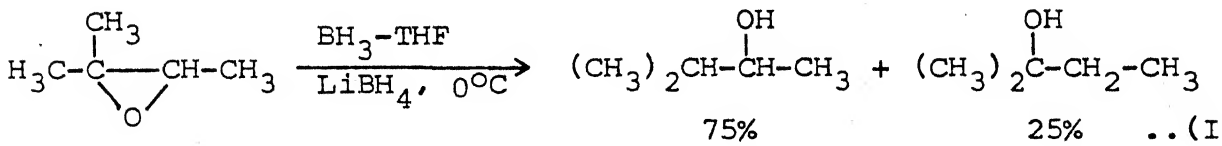
The reaction involving the use of Red-Al seems to involve its initial complexation with -OH, followed by intramolecular H^- attack. The DIBAL reduction also seems to involve initial formation of a complex with -OH, in which aluminium serves as Lewis acid to facilitate intermolecular attack of H^-.

The second class of hydride transfer reducing agents are those based on boron,[8] and again a number of reagents have been developed. Depending upon the nature of the reagent/reagent system, different kinds of selectivities are observed. For example, the reduction of epoxides with diborane gives the less substituted alcohol predominantly. But the reaction is extremely slow[15] and in many cases proceeds with extensive rearrangement.[16] Reaction of 1-methyl cyclohexene oxide (142) with borane-THF at 25°C and subsequent oxidation gives a mixture of 2-hydroxymethyl cyclohexanols (143) (Eqn. II.21)



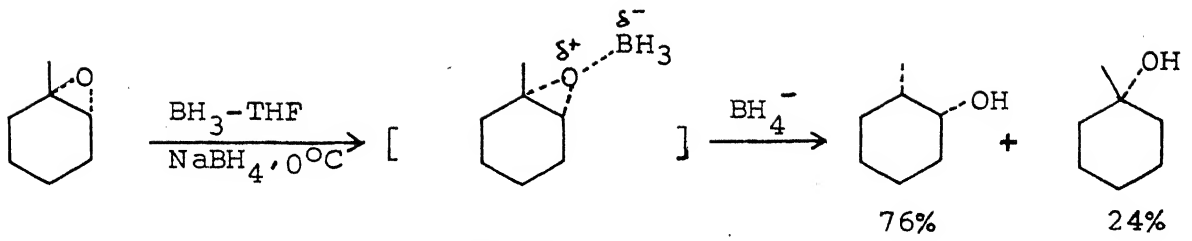
142 143 ..(II.21)

The presence of small amounts of sodium or lithium borohydride greatly increases the rate of reaction of epoxides with diborane and results in the formation of mono-alcohols in good yields.[17] The reaction involves anti-Markonikoff opening of the epoxide ring giving less substituted alcohols (Eqn. II.22).



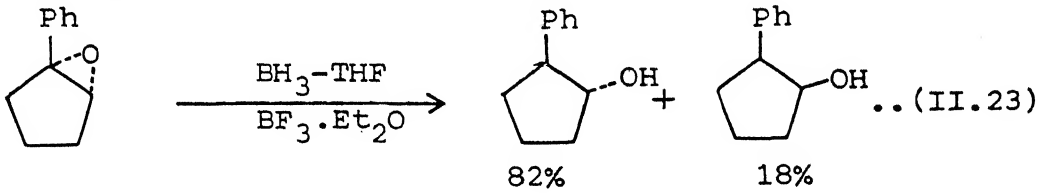
..(II.2

With 1-alkyl cycloalkene oxides, cis-2-alkyl cycloalkanols are formed and thus this method complements the hydroboration-oxidation of cycloalkanes which leads to trans-2-cycloalkanols (Scheme II.43).



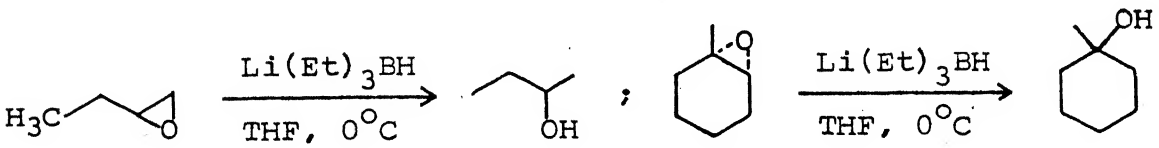
SCHEME II.43

Reduction of epoxides derived from arylethenes with BH_3-THF in the presence of $BF_3.Et_2O$ also results in anti-Markonikoff ring opening to give high yields of the corresponding less substituted mono-alcohols (Eqn. II.23):[18]



..(II.23)

Trialkyl borohydrides have emerged in recent years as highly selective reducing agents. Unlike the parent compound, i.e., lithium borohydride, which reduces epoxides slowly, triethyl borohydride (also referred to as "super hydride") reduces epoxides almost quantitatively to alcohols with exceptional regio- and stereoselectivity.[19] Thus 1,2-epoxybutane (143) gave 2-butanol (144) and 1-methyl cyclohexeneoxide (142) gave 1-methyl cyclohexanol exclusively (Scheme II.44).[21]

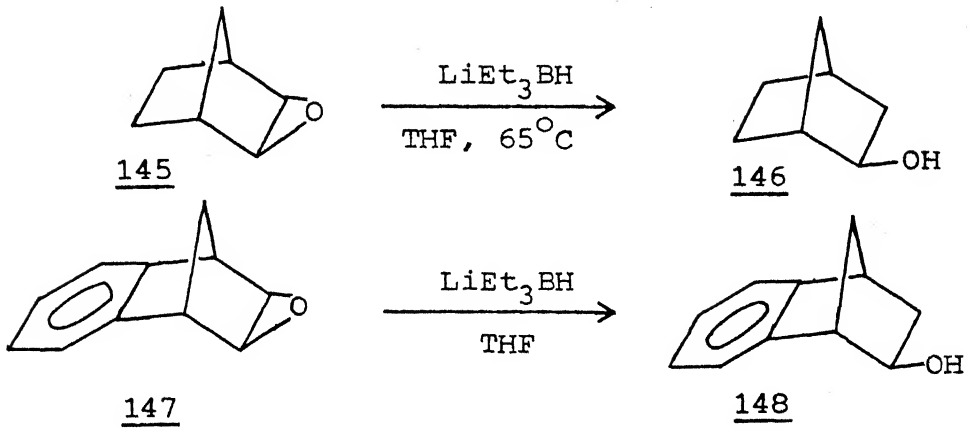


143 144 142

SCHEME II.44

Bicyclic epoxides like norborneneoxide (145) and benzonorborneneoxide (147), which are resistant to usual reducing

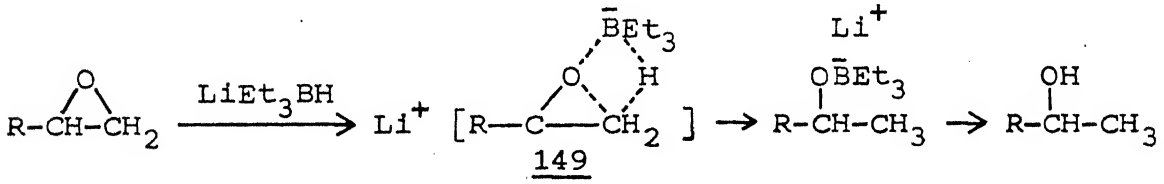
agents and prone to rearrangement are neatly reduced by lithium triethylborohydride to single alcohols 146 and 148, respectively (Scheme II.45).



145 146 147 148

SCHEME II.45

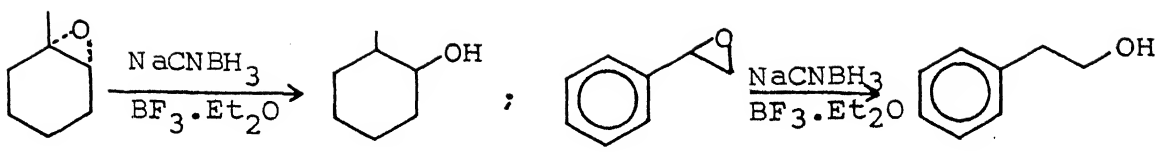
In case of unsymmetrical epoxides, the reduction with lithium triethylborohydride, gives the more substituted alcohols, clearly demonstrating an S_N2 mode of attack by H^-. Kinetic study indicates that the reduction of epoxides is indeed a bimolecular reaction, and the mechanism involves a four centred transition state 149 (Scheme II.46).[20]



149

SCHEME II.46

A combination of sodium cyanoborohydride and $BF_3.Et_2O$ in THF reduces epoxides chemoselectively and in a regioselective manner to give the less substituted alcohols.[22] The regioselectivity is controlled by hydride trapping at the site of more stable carbonium ion (S_N1) (Scheme II.47).

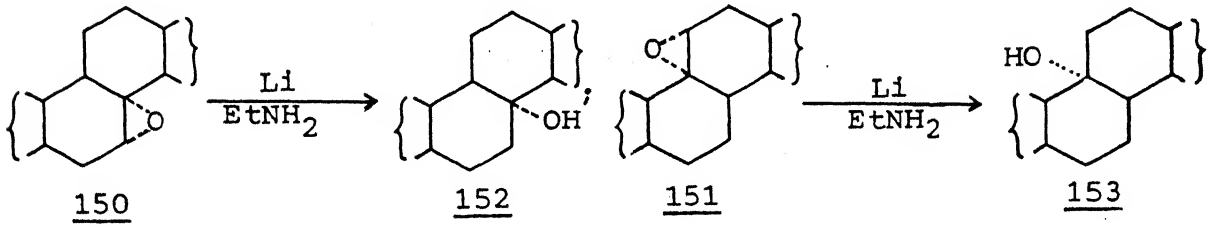


SCHEME II.47

This reagent is, however, unsuitable for epoxides which are prone to Lewis acid induced rearrangement.

(b) Metal-amine reductions:

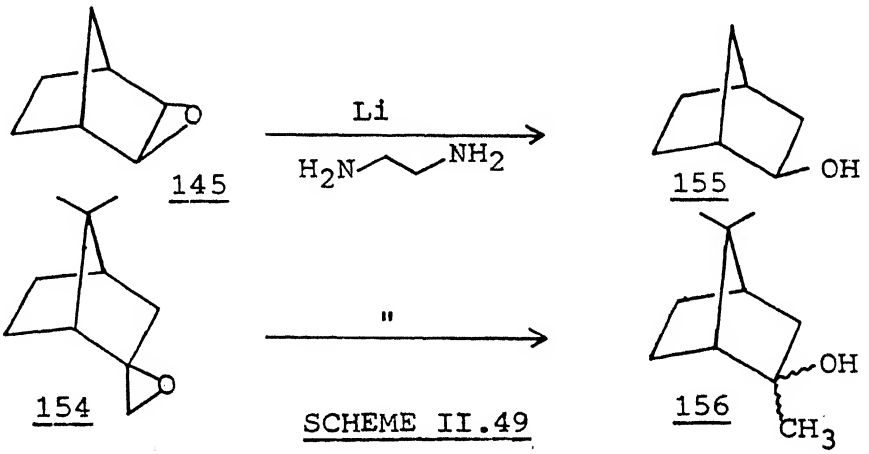
Much work has been carried out on the use of alkali metals, especially lithium, for the reduction of epoxides to alcohols. Liquid ammonia, ethylamine and ethylenediamine have typically been used as solvents for this reaction. Lithium in ethylamine is reported to be a superior reagent for the reduction of sterically hindered steroidal epoxides to axial alcohols.[23] Thus, 7α:8α, 150, and 9α:11α, 151, epoxides, which are not reduced by lithium aluminium hydride, are converted to 8α, 152, and 9α, 153, alcohols, respectively in high yields (Scheme II.48) by using lithium ethylamine combination.



150 152 151 153

SCHEME II.48

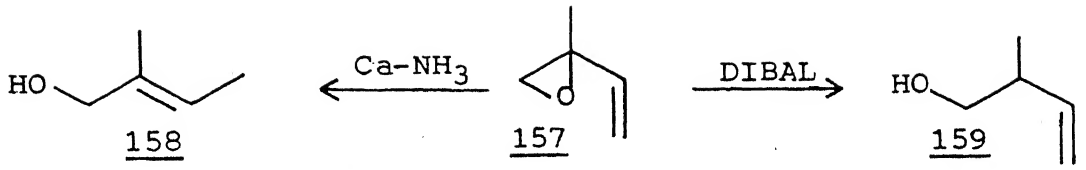
Lithium in ethylenediamine has been used for the reduction of non-steroidal epoxides. It is reported[24] to be especially suitable for the clean reduction of hindered and unstable epoxides which are prone to rearrangement. Thus, norbornene-oxide(145)and the labile and hindered 2-methylene-7,7-dimethyl-bornane oxide(154)were reduced to the corresponding secondary and tertiary alcohols 155 & 156, respectively (Scheme II.49).



SCHEME II.49

The ease of reduction of sterically hindered epoxides by metal-amine reductions, is attributed to the low steric requirement of solvated electrons, which essentially are the nucleophiles that bring about the reduction.

α,β-Unsaturated epoxides are reduced with concomittant allylic rearrangement, to give allylic alcohol with E-configuration of the double bond.[25] This is in contrast to DIBAL reduction which leads to allylic alcohol with Z-configuration. Thus, for example, reduction of epoxide 157 with calcium-ammonia gives 158 while with DIBAL 159 is obtained (Scheme II.50).

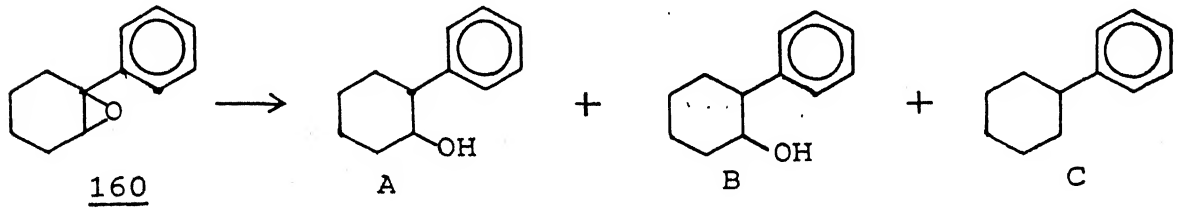


158 157 159

SCHEME II.50

(c) Catalytic hydrogenation:

Most epoxides undergo hydrogenolysis in the presence of a catalyst, affording as principal product an alcohol or a mixture of alcohols.[26] The catalysts commonly used are Raney-Nickel (Ra-Ni), palladium on carbon (Pd-C), platinum dioxide (PtO_2) or platinum black (Pt). The direction of cleavage of the C-O bond of epoxide depends on substrate structure, catalyst and reaction conditions. Hydrogenation of 1-phenyl-7-oxabicyclo-[4,1,0]heptane (160) provides an illustration (Scheme II.51).[27]



160 A B C

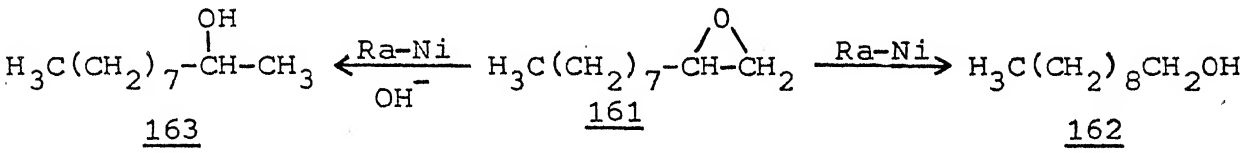
Catalyst	Amount of Catalyst (mmol)	NaOH (mmol)	A % (trans)	B % (cis)	C %
Ra-Ni	1.0	-	30	11	59
Ra-Ni	1.0	1.0	5	93	2
Pd-C	0.1	-	3	93	4
Pd-C	0.1	1.0	-	100	trace

SCHEME II.51

Both Pd-C and Ra-Ni open the hindered benzyl C-O bond, Pd with inversion in configuration and Ra-Ni in neutral medium primarily with retension of configuration. Addition of alkali changes the

stereochemistry of ring opening and curtails excessive deoxygenation.

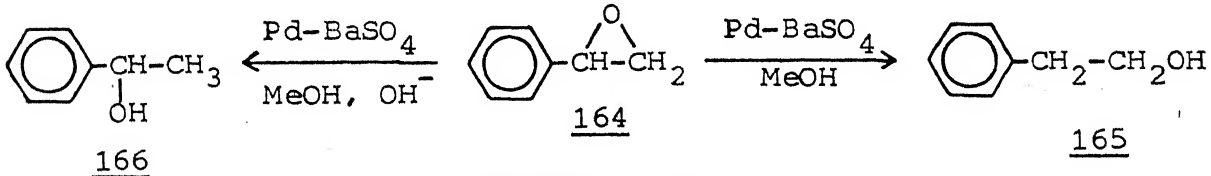
Both regio- and stereospecificity are influenced by the presence or absence of a base. Thus, hydrogenation of 1,2-epoxydecane (161) over Ra-Ni without base affords mainly 1-decanol (162), while in the presence of a base affords mainly 2-decanol (163) (Scheme II.52).



163 161 162

SCHEME II.52

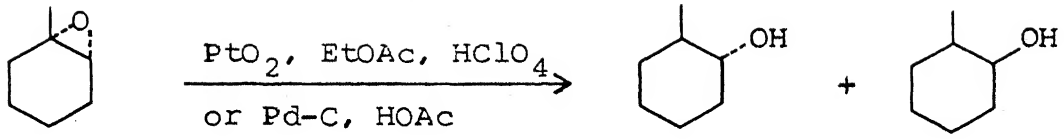
Hydrogenation of styrene oxide over Pd-C[29] or over Pd-$BaSO_4$ in methanol gives 2-phenyl ethanol (165) while in buffered alkaline methanol gives 1-phenyl ethanol (166) (Scheme II.53).[30]



166 164 165

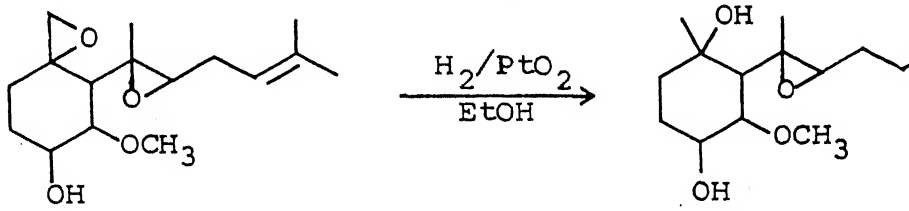
SCHEME II.53

In acid medium the epoxide ring opens at the more substituted carbon (so as to afford more stable carbocation). Thus, hydrogenation of 1-methyl cyclohexeneoxide over PtO_2 in the presence of $HClO_4$, or Pd-C in acetic acid afford cis and trans 2-methyl cyclohexanols (Scheme II.54).[31]



SCHEME II.54

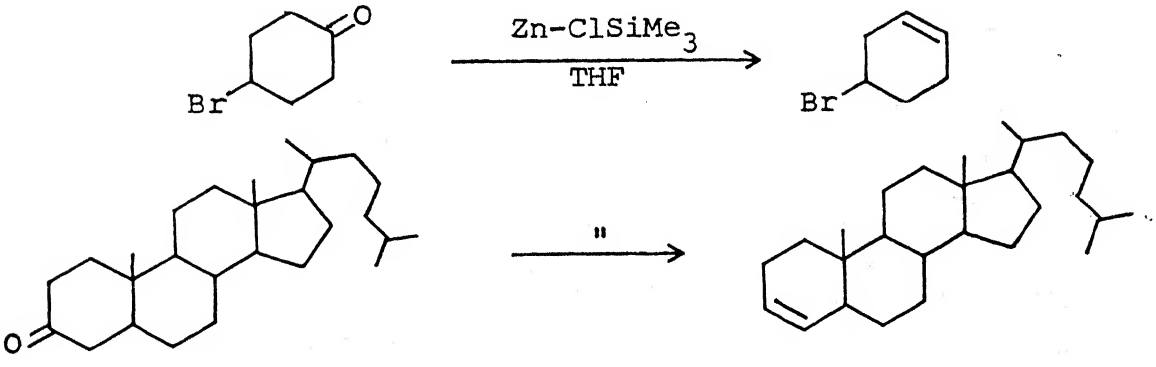
In neutral medium with PtO_2, a non-activated epoxide may open at the carbon bearing fewest substituents. Thus, the diepoxide 167 derived from fumigallin, on hydrogenolysis over PtO_2 in EtOH afforded 168 by selective C-O bond cleavage at the least substituted carbon atom (Eqn. II.24).[32]



167 168 ..(II.24)

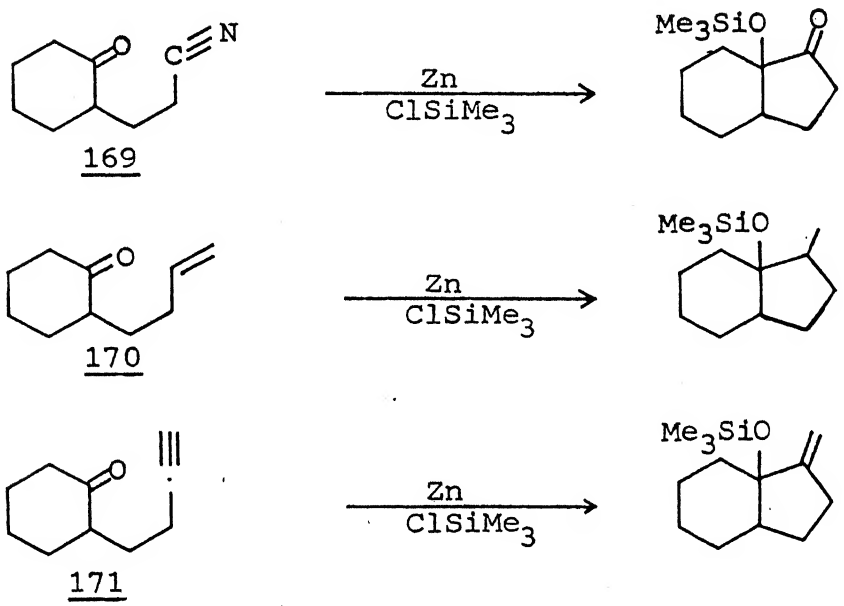
II.B.1(ii) Present Work

Reduction of epoxides into corresponding alcohols by using a variety of reducing agents has been reported in the literature, a brief review of which is presented in the background part of this section. It is apparent that all the reagents (except metal-ammonia and catalytic hydrogenation) make use of their hydride donating ability to bring about such reductions. These hydride containing reagents are also capable of reducing a variety of other functional groups such as carbonyl groups, esters etc. In the present study we have found that a combination of zinc-chlorotrimethylsilane ($Zn\text{-}ClSiMe_3$) provides an extremely mild reagent system which converts epoxides into alcohols very rapidly and in high yields. This reagent system was first used by Motherwell[33] for the conversion of ketones to olefins. A few example studied by them are mentioned in Scheme II.55.



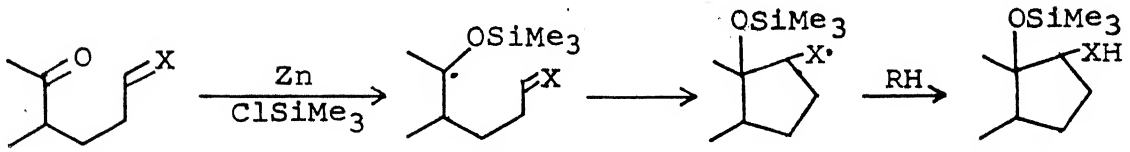
SCHEME II.55

According to Motherwell, the mechanism of this reaction is not clear. However, recently Corey et al.[34] have applied this reaction for intramolecular cyclization of a variety of ω-ketonitriles 169, ω-ketoolefins 170, ω-ketoacetylenes 171 etc. (Scheme II.56)



SCHEME II.56

and they believe that such transformations proceed via an electron transfer process, as shown in Scheme II.57.



SCHEME II.57

Besides the above mentioned reports, Zn-$ClSiMe_3$ has also been utilized in the reduction of sulphoxides to sulphides by

Schmidt et al.[35]

All the above reported reactions were carried out by the use of an excess of Zn-$ClSiMe_3$ in refluxing THF for an extended period of time.

In the present study, a variety of epoxides were found to undergo reduction into the corresponding alcohols at room temperature within 5 minutes, in yields ranging from 80-98% (Table II.4). Substrates chosen for this study included three symmetrical 171-173 and three unsymmetrical 174-176 epoxides. It was found that unsymmetrical epoxides yielded the less substituted alcohol as the major product (Eqn. 11.25):

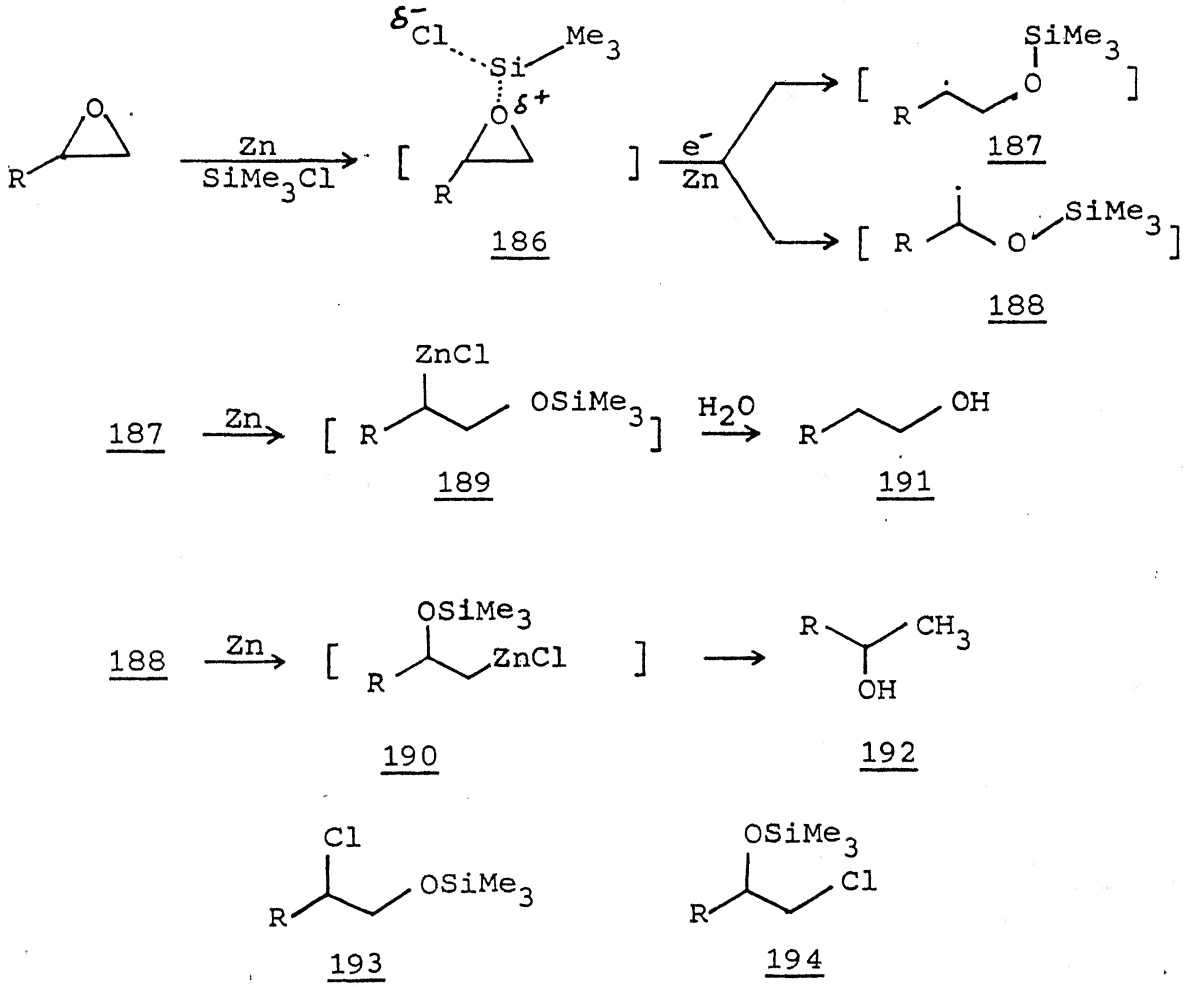
$$R\text{-}CH(O)CH_2 \xrightarrow[CH_2Cl_2]{Zn\text{-}ClSiMe_3} \underset{\text{major}}{R\text{-}CH_2\text{-}CH_2\text{-}OH} + \underset{\text{minor}}{R\text{-}CH(OH)\text{-}CH_3} \qquad ..(II.25)$$

Cyclopentene oxide (171) was reacted with an excess of zinc dust and $ClSiMe_3$ in dichloromethane at room temperature for 5 minutes to obtain cyclopentanol (177) in 80% yield (b.p. 75°C/ 25 mm; lit.[38] b.p. 185°C) whose IR spectrum (neat showed absorption at 3360 cm^{-1} (ν_{O-H}). Similarly, cyclohexene oxide (172)and cycloheptene oxide (173) reacted to give cyclohexanol(178)(b.p. 160-161°C; lit.[38] b.p. 161°C). IR: ν_{O-H} at 3350 cm^{-1}) and cycloheptanol (179)(b.p. 95°C/25 mm; lit.[38] b.p. 185°C, ν_{O-H} at 3350 cm^{-1}) in 98% and 83% yields, respectively. On the other hand, 1-octene oxide (174),gave a mixture of two octanols 180 and 181 in 88% yield in the ratio 65:35 as was evidenced by its gas

chromatographic (GC) analysis (SE-30 column at 200°C), by comparison with authentic sample. Attempts to separate the mixture by a bulb to bulb distillation set up were not successful. IR spectrum of the mixture showed broad absorption at 3400 cm^{-1} for ν_{O-H} and ^1H NMR spectrum showed absorptions at δ 0.67-1.0 (m, methyl protons), 1.03-1.06 (m, methylene protons) and 3.33-4.0 (m, -OC<u>H</u> and -OC<u>H</u>$_2$). It was difficult to determine the ratios of the two alcohols <u>180</u> and <u>181</u> from the ^1H NMR spectrum. Similarly 1-undecene oxide <u>175</u> under similar conditions gave a mixture of 1- and 2-undecanols <u>182</u> and <u>183</u> in 96% yield (IR: ν_{O-H} at 3400 cm^{-1}) in the ratio 69:31 as evidenced by GC analysis. Finally cis-2-octene oxide (<u>176</u>) under similar reaction conditions also gave a mixture of 2- and 3-octanols <u>184</u> and <u>185</u> in 97% yield (IR: ν_{O-H} at 3380 cm^{-1}) in the ratio 59:41 as determined by GC analysis. Again in both these cases it was not possible to separate the alcohols by distillation.

The ^1H NMR of the mixture of <u>182</u> and <u>183</u> alcohols showed absorptions at δ 0.68-1.03 (m, methyls), 1.06-1.93 (m, methylene protons) and 3.44-3.84 (m, -OC<u>H</u> and -OC<u>H</u>$_2$) and the ^1H NMR of the mixture of <u>184</u> and <u>185</u> showed absorptions at 0.9 (t, methyls), 1.03-1.87 (m, methylene protons), 3.3-4.22 (m, -OC<u>H</u>-). Although from the NMR spectra of the mixtures it was not possible to determine the ratio of the isomeric alcohols, but from the GC analysis their relative percentages could be determined (SE-30 column was used at oven temperature 250°C) by comparison with authentic samples.

The above set of experiments clearly indicated the formation of the less substituted alcohol as the major product. A probable mechanism for the preferred formation of the less substituted alcohol is shown in Scheme II.58. The epoxide oxygen, upon coordination with $ClSiMe_3$, may lead to the formation of the intermediate 186, which then receives an electron from zinc to form intermediates 187 and 188:

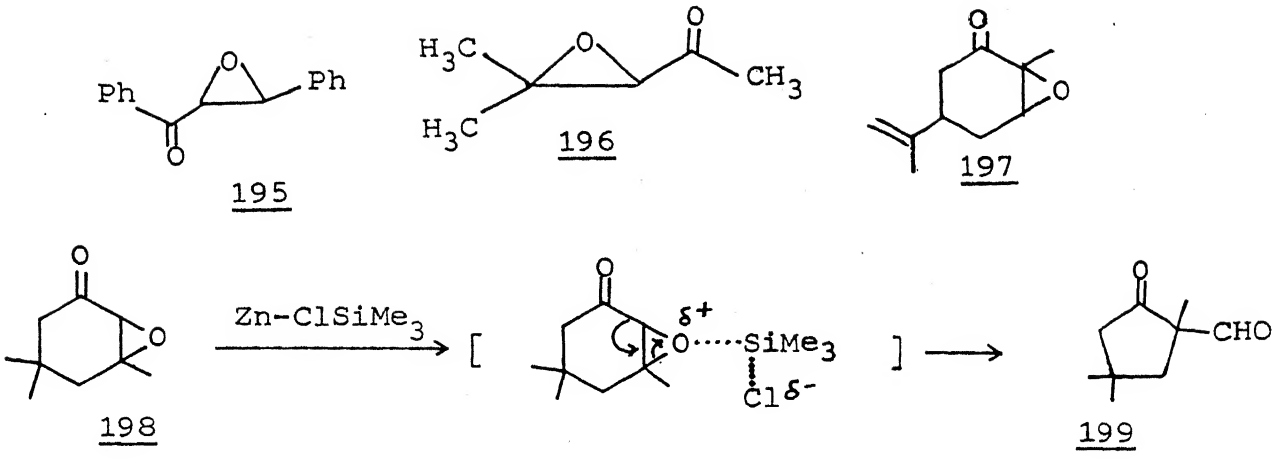


SCHEME II.58

The relative stability of these intermediate then decides the

ratio of the two alcohols 191 and 192. It is obvious that a more substituted radical would form in the higher ratio than the less substituted one because of its greater stability. These intermediates then again receive another electron from zinc to form the organozinc compounds 189 and 190 which eventually lead to the formation of the corresponding alcohols upon work-up. The possibility of formation of compounds 193 and 194 is completely ruled out as no chlorohydrins were formed. Further, it is well known in the literature[36] that epoxides react with $ClSiMe_3$ only at high temperature (100°C) to form chlorosiloxanes.

Thus the reduction of simple epoxides with Zn-$ClSiMe_3$, as described above, appears to be a simple alternative over other reducing agents for such a conversion. In order to further explore the scope of this reduction, we studied the reactions of 2,3-epoxy ketones. However, the reactions in this case were not clean and a number of products were formed. Thus, chalcone epoxide (195), mestyl oxide (196) and epoxy carvone (197), all gave a number of products upon reaction with Zn-$ClSiMe_3$ whose purification was found to be difficult. Interestingly, when isophorone epoxide (198) was reacted with Zn-$ClSiMe_3$, a ring contracted product 199 (Scheme II.59) was obtained in 76% yield, b.p. 70°C/7 mm (lit.[42] b.p. 49-50°C/2 mm). The structure of this product was confirmed by its spectral characteristics. Infrared spectrum of this compound showed a strong absorption at 1720 cm^{-1} (br, s, $\nu^{H}_{C=O}$ and $\nu_{C=O}$) and also at 2870 cm^{-1} and

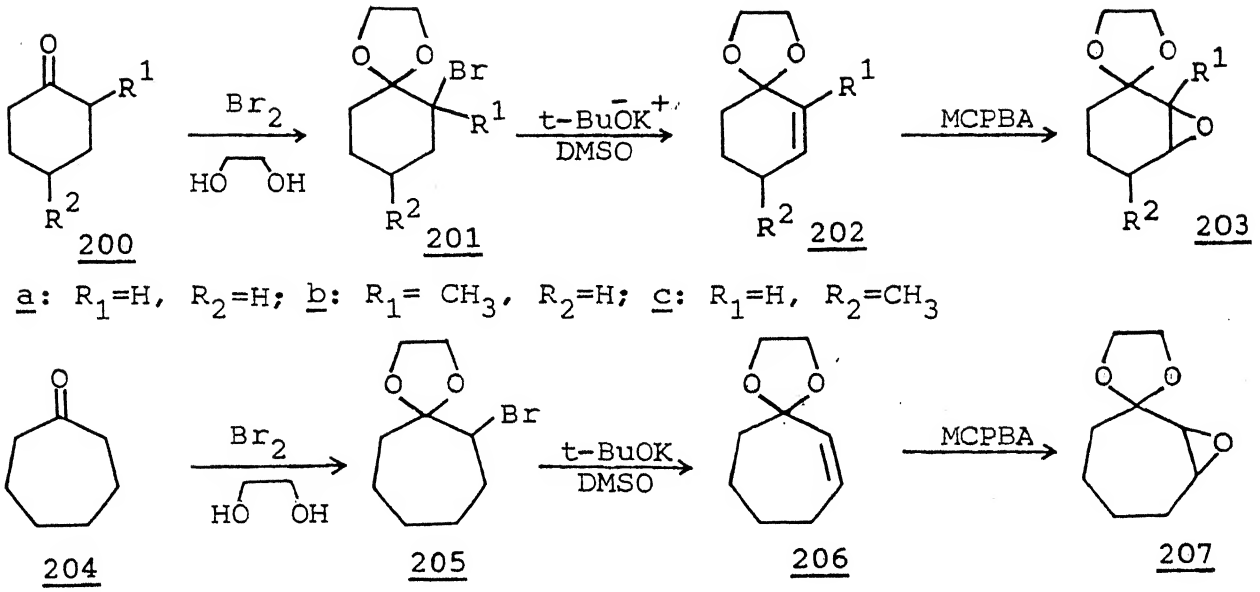


SCHEME II.59

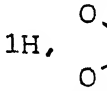
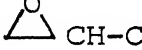
2900 cm^{-1} (C-H stretching bands of -CHO) and its ^1H NMR spectrum showed absorptions at δ 0.95 (s, 6H, gem-CH_3), 1.16 (s, 3H, H_3C-C(-)-CO), 1.32 (s, 2H, CH_2-C(-)-CHO), 2.54 (s, 2H, -CH_2CO), 9.86 (s, 1H, CHO). The mass spectrum showed M^+ peak at 154.

Since the reduction of 2,3-epoxy ketones did not lead to clean products, further studies were carried out with 2,3-epoxy ketals, in order to examine: (i) whether the ketal group remains unaffected, and (ii) whether any regioselectivity is observed in the reduction. The substrates 200a, 200b, 200c and 204 chosen for the study were prepared as shows in Scheme II.60. Bromoketalization of ketones 200(a-c) and 204 gave the corresponding bromo ketals 201(a-c) and 205 which were reacted with t-BuO^-K^+ in dry DMSO to obtain the corresponding olefins 202(a-c) and 206 in 80%, 70%, 78% and 75% yields, respectively. The structures of the olefinic ketals were confirmed by their spectral data (cf. Sec. II.B.1(iii) for spectral details).

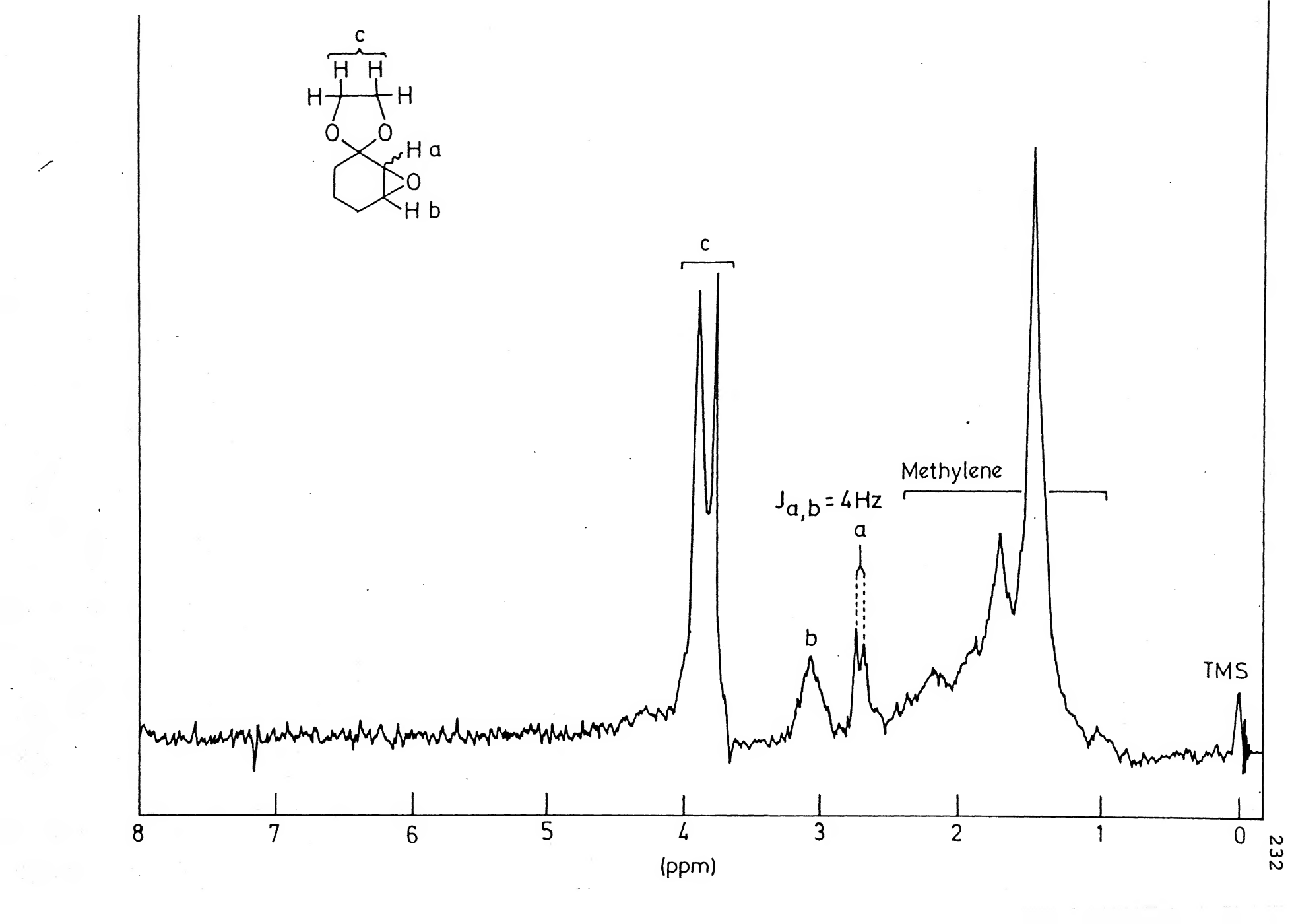
Oxidation of the olefinic ketal 202a with m-chloroperbenzoic acid (MCPBA) at room temperature gave the epoxy ketal 203a

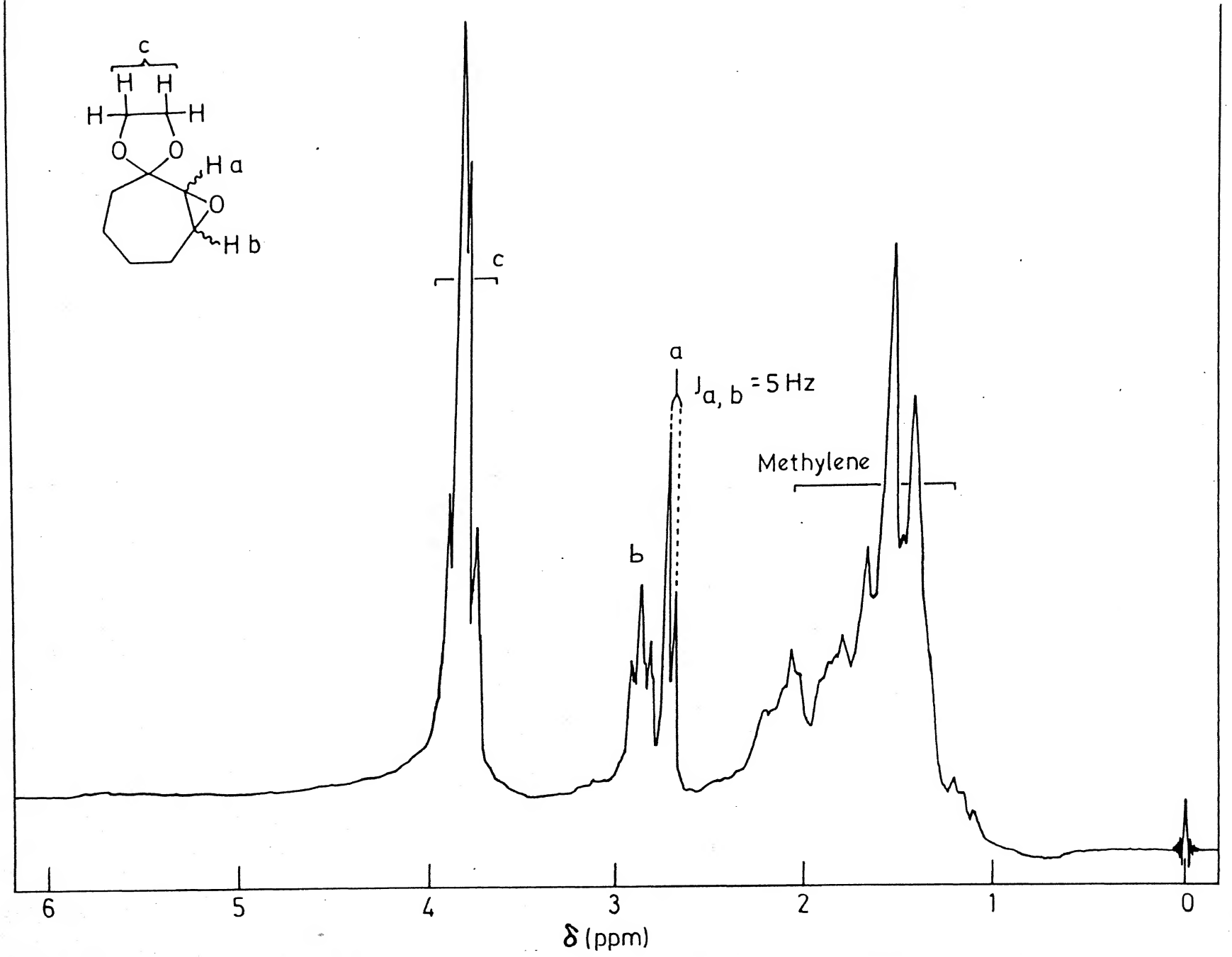


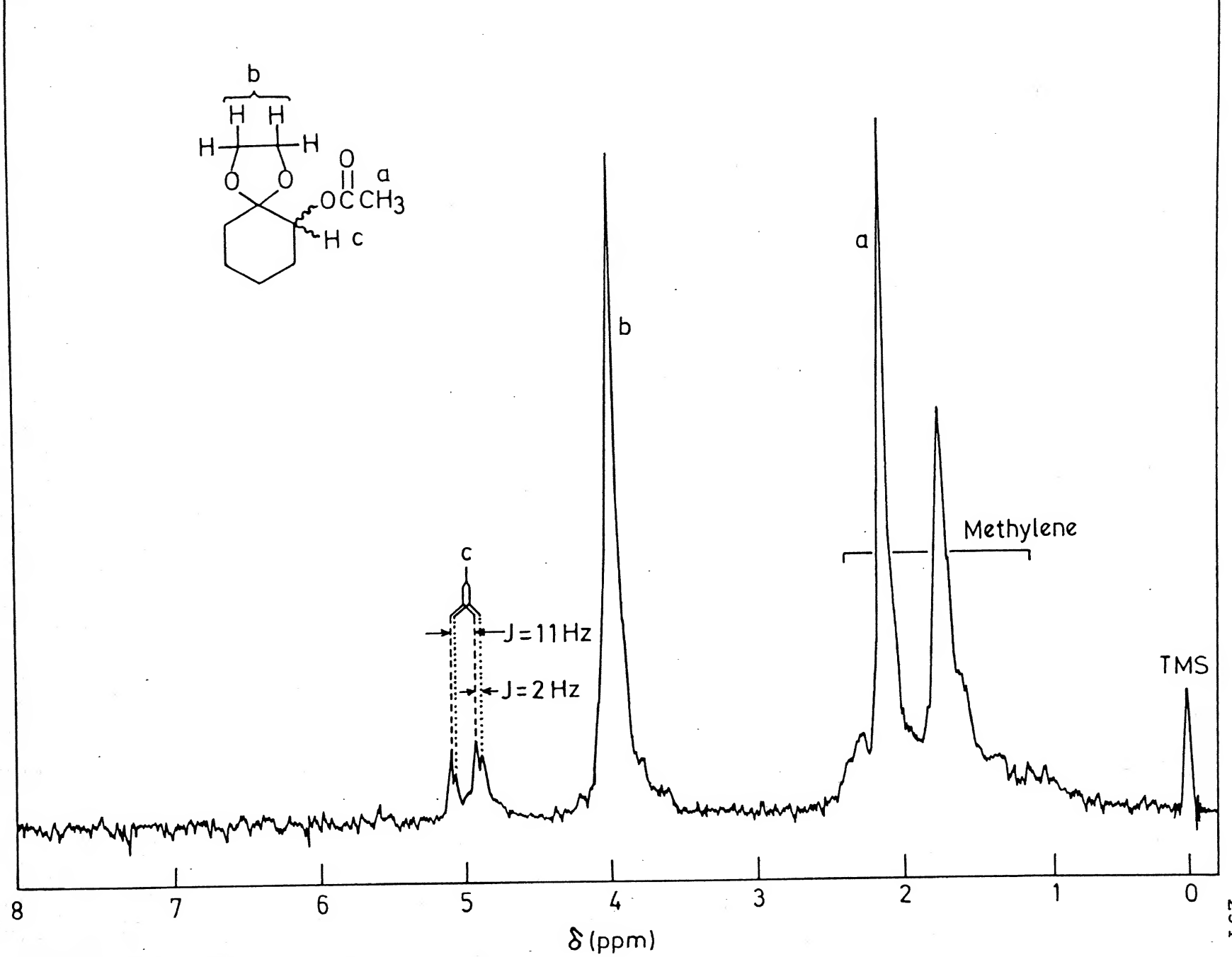
SCHEME II.60

b.p. (oil bath temp.) 100-105°C/2 mm in 92% yield. Its IR spectrum showed absorption at 1120 cm^{-1} (ν_{C-O-C}) and 1270 cm^{-1} (ν) whereas ^1H NMR spectrum showed absorptions at δ 1.1-2.4 (m, 6H, $-(CH_2)_3-$), 2.73 (d, 1H,  , J = 4 Hz), 2.64-2.79 (m, 1H, ) and 3.33-3.73 (m, 4H, $-OCH_2-CH_2-O-$). Its mass spectrum showed M^+ peak at 156. In a similar fashion epoxidation of the olefinic ketals 202b, 202c and 206 gave the epoxides 203b, 203c and 207 in yields 81%, 91% and 80%, respectively. Their spectral characteristics (as reported in Sec. II.B.1(iii)) are in conformity with the structures assigned to them.

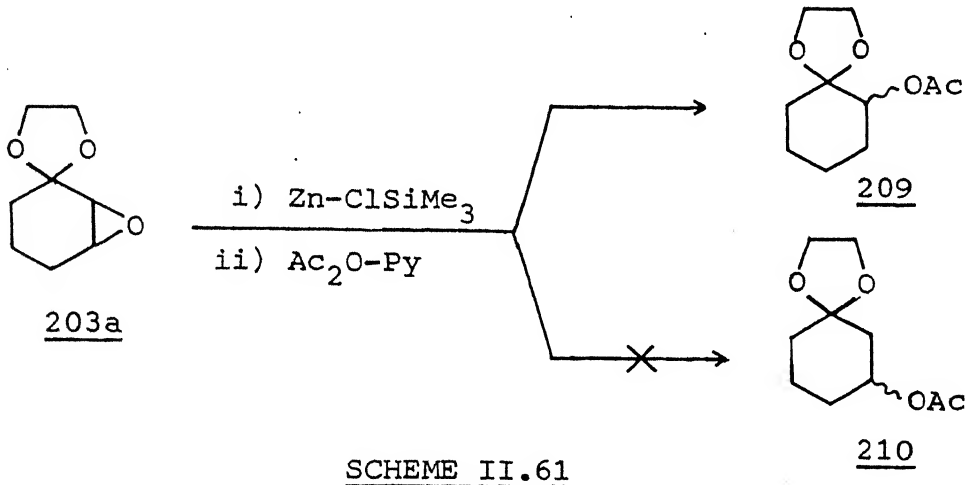
Reduction of these epoxy ketals with Zn-$ClSiMe_3$ was then carried out at 0°C. Thus the epoxy ketal 203a on reaction at 0°C for 10 mins. gave an hydroxy ketal (IR: 3480 cm^{-1}, ν_{O-H}), which was purified as acetate by acetylation with acetic anhydride-pyridine. The structure of this acetate 210 (obtained in 82%


c
H H
H H
O O
H a
O
H b
c
Methylene
$J_{a,b}$ = 4Hz
a
b
TMS
8
7
6
5
4
3
2
1
0
(ppm)


c
H H
H H
O O
H a
O
H b
c
a
$J_{a,b}$ = 5 Hz
Methylene
b
6
5
4
3
2
1
0
δ (ppm)


b
H H
H H
O O
O
a
OCCH3
H c
a
b
c
J = 11 Hz
J = 2 Hz
Methylene
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

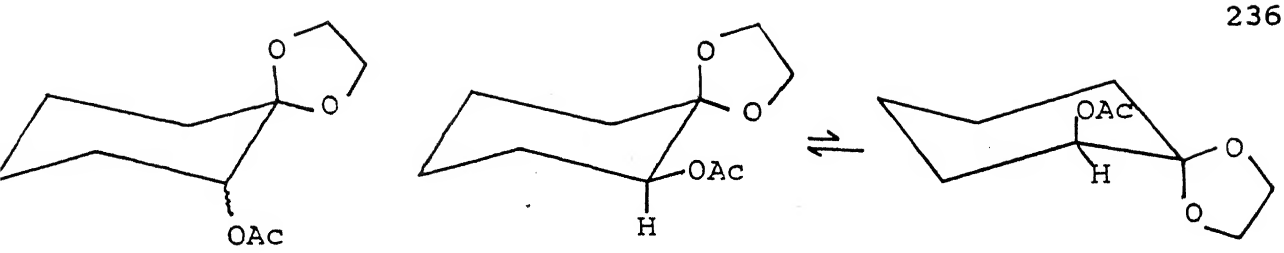
overall yield) was confirmed from its spectral characteristics. Its IR spectrum showed a strong absorption at 1760 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and its ^1H NMR spectrum indicated absorptions at δ 1.33-2.33 (m, 8H, 4 CH_2's), 2.0 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 3.87 (s, 4H, $-OCH_2-CH_2-O-$) and 4.9 (dd, 1H, CH-OAc, J = 11 Hz and 2 Hz). Mass spectrum of it showed M^+ peak at 200. The two possibilities of the epoxide ring opening (Scheme II.61) were expected to give compounds 209 and 210, upon acetylation. Compound 210 should show a distinct multiplet



203a 209 210

SCHEME II.61

for the methine proton α- to the -OAc group (-CH-OAc) in its ^1H NMR spectrum due to its being coupled to the two sets of methylene protons on either side. However, the observed ^1H NMR spectrum of the only product obtained in this reaction showed a doublet of doublet corresponding to the methine protons at δ 4.9, with coupling constants of 11 Hz and 2 Hz (cf. Fig. II.14). This could be expected only from the structure 209 assigned to this compound. Further, this compound appears to be a mixture of the two stereoisomers 209a and 209e (Scheme II.62) in the ratio 64:36



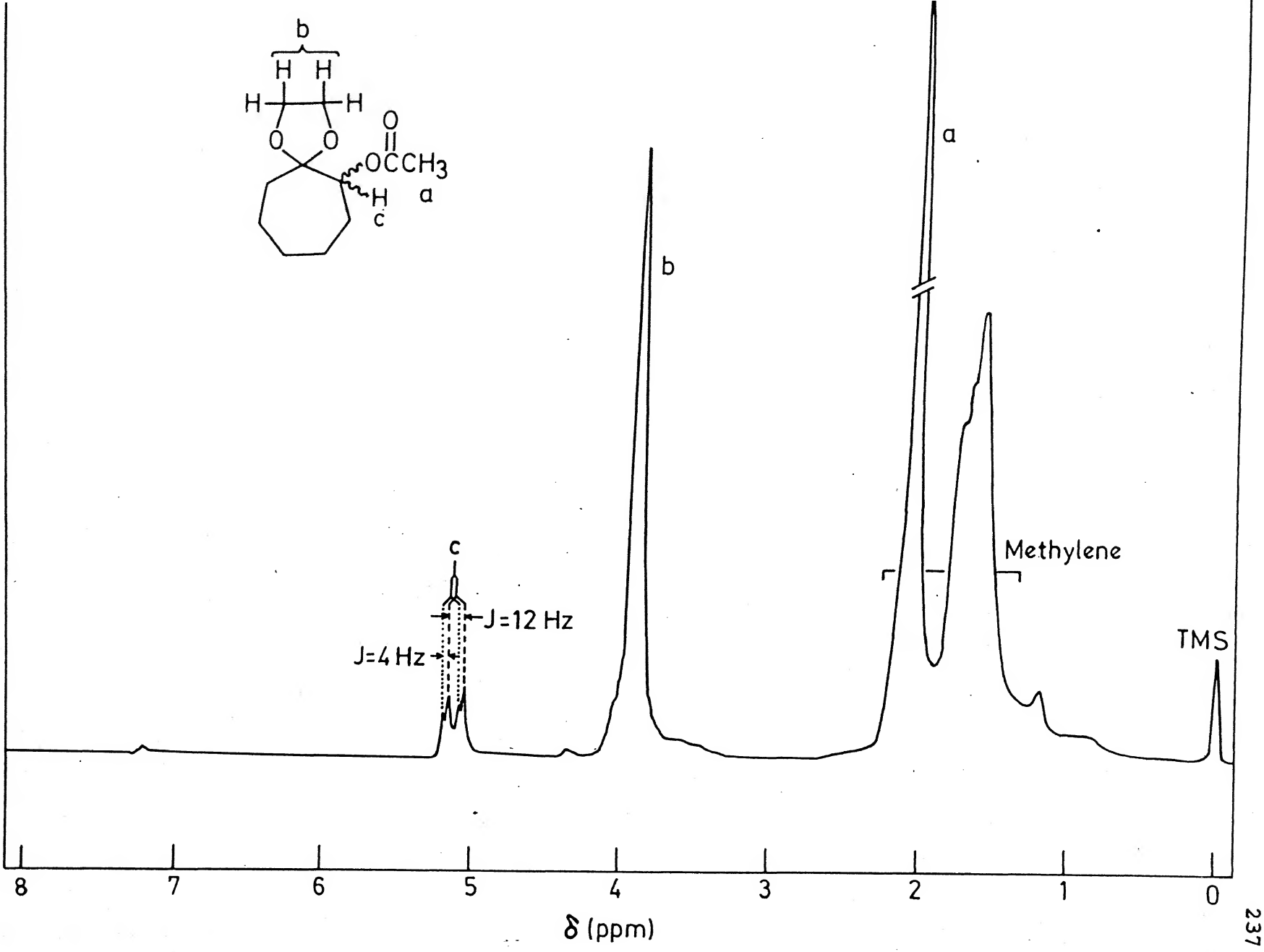
209 209e 209a

-OAc equitorial (64%) -OAc axial (36%)

SCHEME II.62

as determined from the Eliel equation ($W = W_{aa}.n + W_{ee}(n-1)$; n = mole fraction of the equatorial conformation, and W = observed bandwidth = 11 Hz + 2 Hz = 13 Hz) by substituting the standard values of W_{aa} and W_{ee} (15.7 Hz and 5.5 Hz, respectively) as reported for any 2-substituted cyclohexylethyleneketals by Mursakulov et al.[37] The predominance of the equatorially substituted product in similar cases, has a precedent in literature,[37] where it has been shown to be an enthalpically favourable conformation.

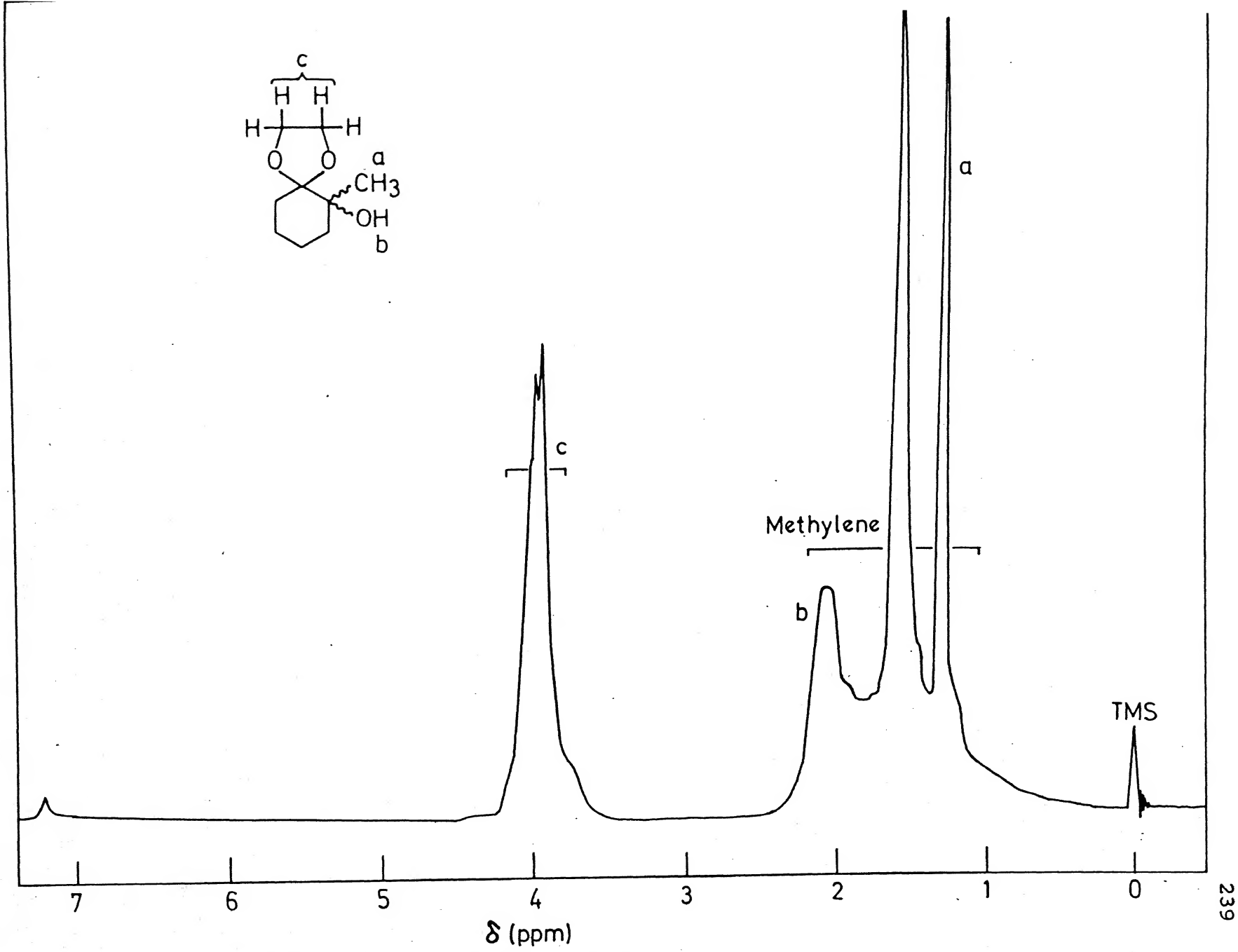
Similarly the epoxy ketal 207 also led to the formation of a single product 211 upon reaction with Zn-$ClSiMe_3$ followed by acetylation in 84% overall yield. Once again on the basis of its spectral data this compound was assigned the structure 211. Thus its IR spectrum showed absorption at 1758 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and its ^1H NMR spectrum showed absorptions at δ 1.32-2.55 (m, 10 H, 5 CH_2's), 2.02 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-\underline{CH}_3$), 3.88 (s, 4H, $-OCH_2-CH_2-O-$) and 5.11 (dd, 1H, $-\underline{CH}-OAc$, J = 12 Hz, 4 Hz). Its mass spectrum showed M^+ peak at 214. From the ^1H NMR spectrum (Fig. II.15) it could be ascertained that the product 211 had the acetate group

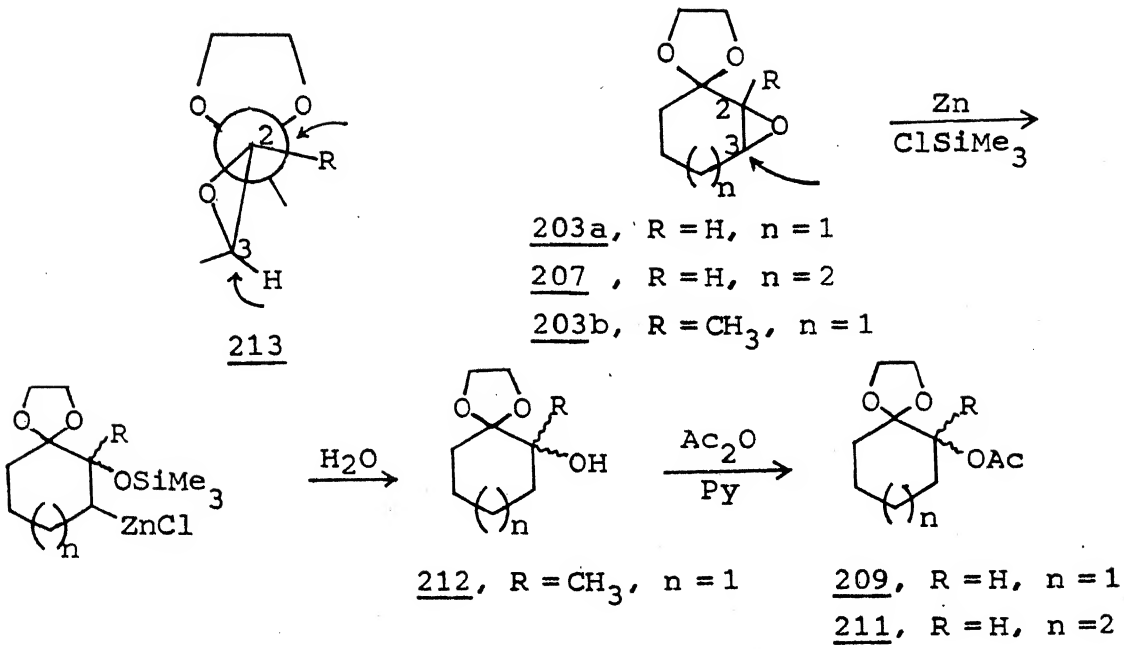

b
H H
H H
O O
O
OCCH3
H a
c
a
b
c
J=12 Hz
J=4 Hz
Methylene
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

α to the ketal unit. The fact that a large coupling constant (12 Hz) is observed in this case for the C<u>H</u>-OAc proton suggested that the vicinal coupling was of the same nature as that of vicinal axial-axial coupling as in the cyclohexane series (i.e., as in compound <u>209</u>, <u>vide supra</u>). The substituent -OAc in this case also appears to be predominantly in the equatorial kind of position, however, the exact percentage of this conformer is difficult to predict since no literature precedent is available for such systems in the cycloheptane series.

In the case of epoxy ketal <u>203b</u> reduction with Zn-$ClSiMe_3$ gave <u>83</u>% of the hydroxy ketal <u>212</u>, which could not be acetylated with Ac_2O-pyridine even after reacting it for a prolonged period (48 hrs.), indicating the hydroxy group to be probably tertiary. This was expected on the basis of the previous two cases studied (viz., epoxides <u>203a</u> and <u>207</u>). The spectral data of this compound confirmed the structure <u>212</u> assigned to it. The presence of -OH group was apparent from its IR spectrum which showed a broad peak at 3500 cm^{-1} (ν_{O-H}). The ^1H NMR spectrum showed absorptions at δ 1.29 (s, 3H, $>C(\underline{CH_3})(OH)$), 1.36 (m, 8H, 4 CH_2's) and 3.72-4.23 (m, 4H, $-OC\underline{H_2}C\underline{H_2}-O-$). The mass spectrum showed M^+ peak at 178.

The above three cases studied, clearly demonstrated that the Zn-$ClSiMe_3$ reduction of such epoxy ketals is a regioselective reaction. This type of regioselectivity could perhaps be explained by considering the steric crowding at the two epoxy carbons (Scheme II.63). Clearly C_2 (cf. <u>213</u>) is sterically more


c
H H
H H
O O
a
CH3
OH
b
c
Methylene
b
a
TMS
7
6
5
4
3
2
1
0
δ (ppm)



213

203a, R = H, n = 1
207 , R = H, n = 2
203b, R = CH_3, n = 1

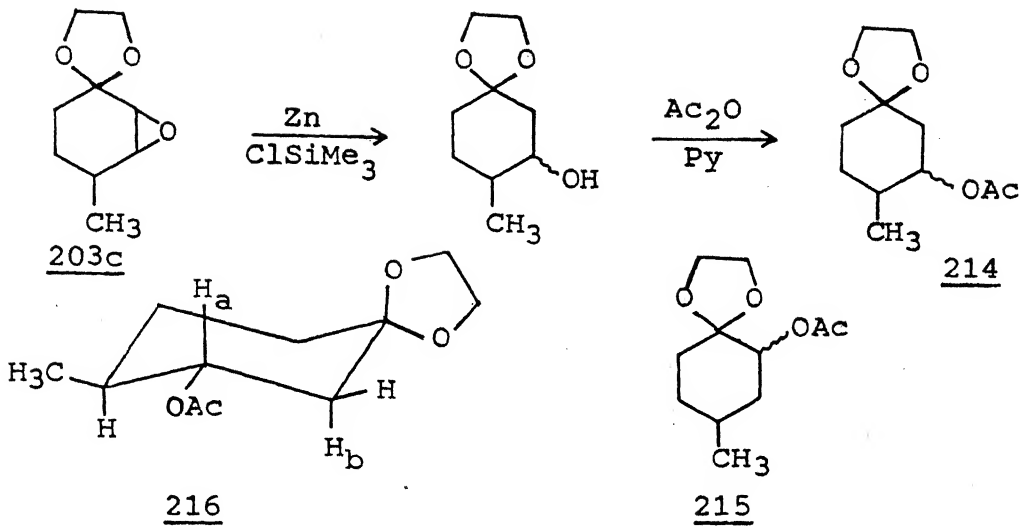
212, R = CH_3, n = 1

209, R = H, n = 1
211, R = H, n = 2

SCHEME II.63

hindered than C_3, and therefore, the observed selectivity is probably found.

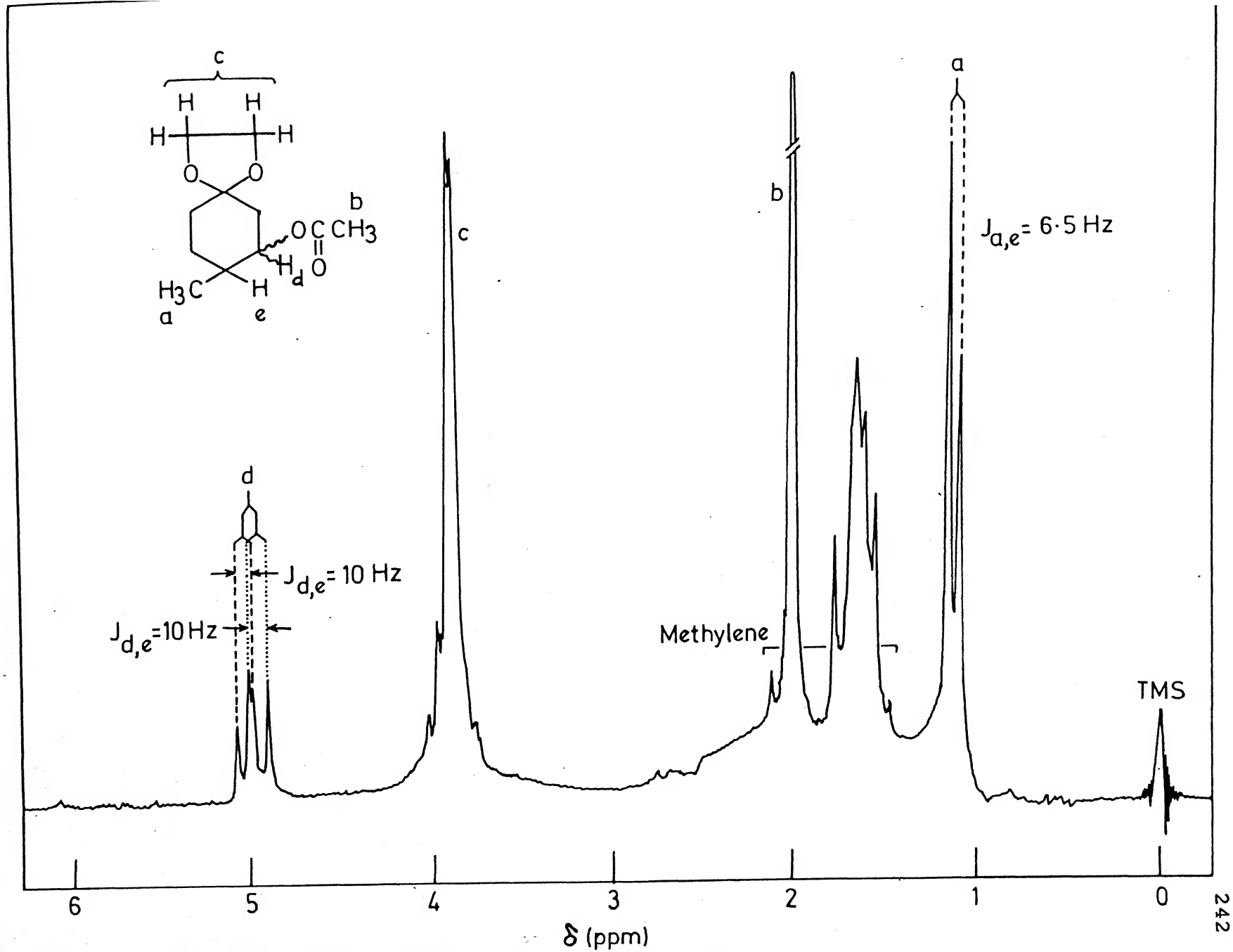
In contrast to the above three examples, reaction of the epoxy ketal 203c with Zn-$ClSiMe_3$, followed by acetylation with Ac_2O-pyridine, surprisingly gave a product which was found to be a 3-acetoxy ketal 214 and not 2-acetoxy ketal 215 (Scheme II.64) as evidenced by its spectral data. Its IR spectrum showed strong absorption at 1755 cm^{-1} (ν_{-OCOCH_3}) and its ^1H NMR spectrum indicated absorptions at δ 1.12 (d, 3H, $-CH_3$, J = 6.5 Hz), 1.62-1.84 (m, 7H, 3 CH_2's and $CH-CH_3$), 2.0 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 3.7-4.1 (m, 4H, $-OCH_2-CH_2-O$) and 4.8-5.1 (m, 1H, -CH-OAc). Its mass spectrum showed M^+ peak at 214. The spin-spin splitting pattern of the methine proton (-CH-OAc), when compared with the spectrum



SCHEME II.64

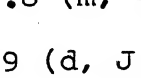
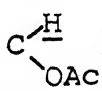
of earlier products 209 and 211 appeared to be of a distinctly different type. In the present case two overlapping doublets each with a coupling constant of 10 Hz were observed (Fig. II. 17). This could be expected only if the methine proton (H_a) is coupled with two axial hydrogens (H_b and H_c) on either side of this carbon (to which H_a is attached). This, therefore, confirms the structure 214 assigned to it. Moreover, from the molecular models the preferred conformation appears to be 216. This example, in which the regioselectivity is reversed as against the cases 203a, 203b and 207 is probably indicative of the fact that the 4-methyl group offers greater steric hindrance relative to the ethyleneketal unit, for the zinc to attack at C_3 carbon.

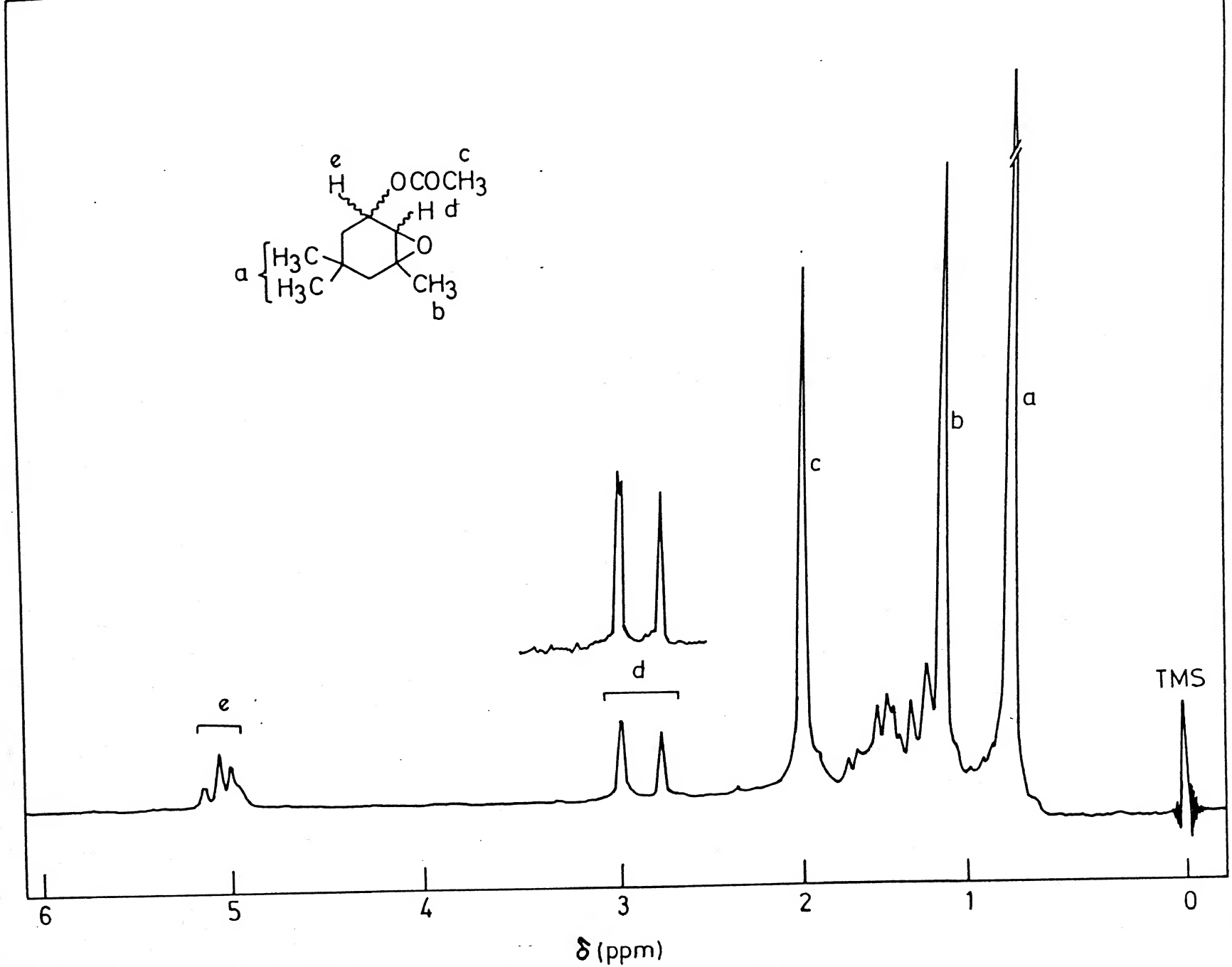
Based on the above studied examples, it appears that Zn-$ClSiMe_3$ is a novel reagent which (i) does not cleave a ketal group under the reaction conditions and (ii) effects regioselective transformation of epoxy ketals into the corresponding reduced

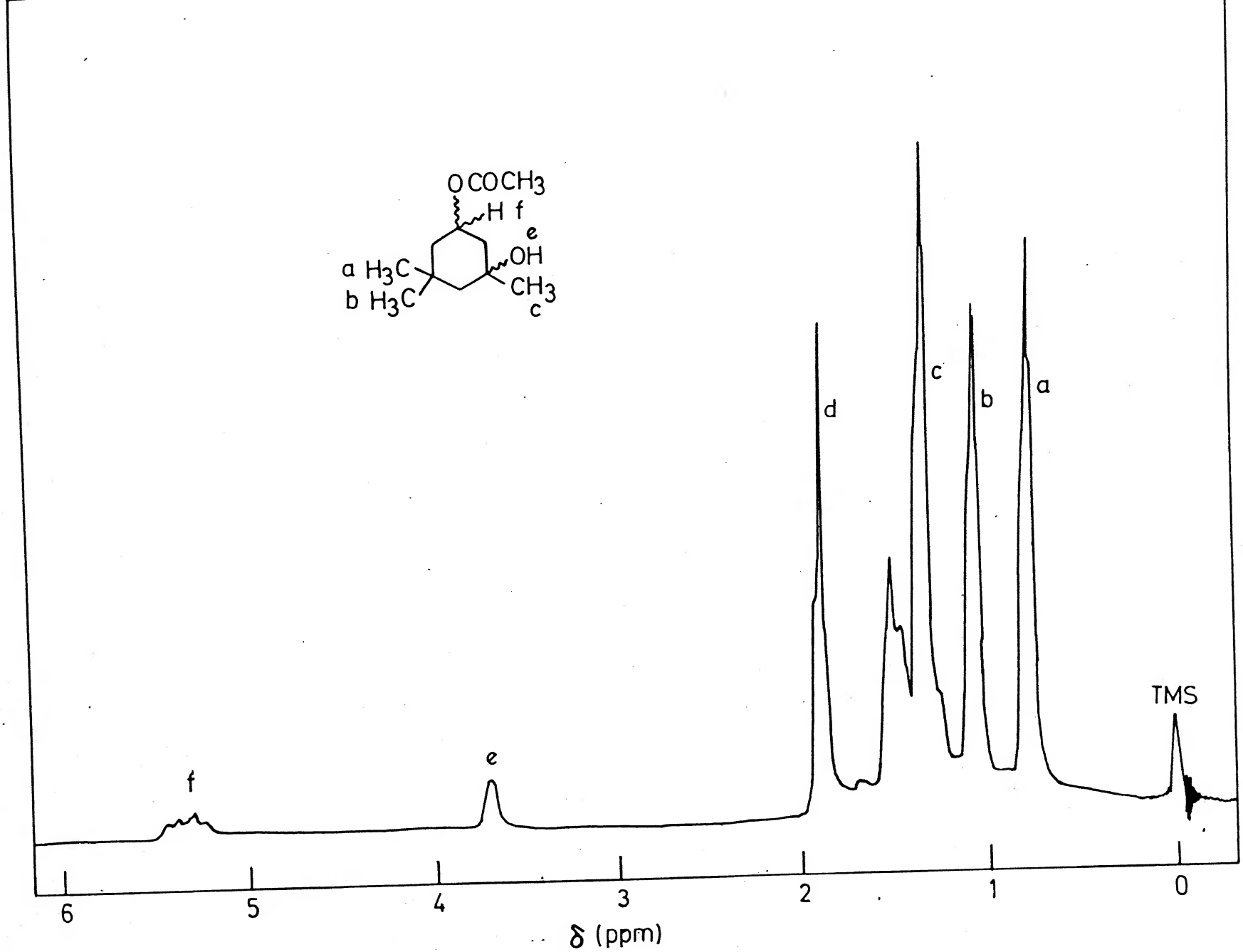

c
H
H
H
H
O
O
b
O C CH3
O
Hd
H3C
H
a
e
d
Jd,e= 10 Hz
Jd,e=10 Hz
c
b
a
Ja,e= 6·5 Hz
Methylene
TMS
6
5
4
3
2
1
0
δ (ppm)

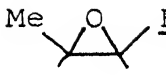
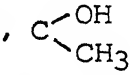
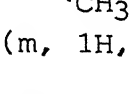
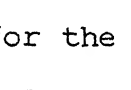
products, the regioselectivity probably being guided by the steric factors.

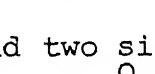
Another set of substrates chosen for reduction with $Zn\text{-}ClSiMe_3$ included 2,3-epoxy acetates 217 to 220. These substrates were chosen with a view to find out (i) if the acetate groups are stable under the reduction conditions, and (ii) if the acetate groups exert any influence on the regiochemistry of the reduction ring opening of the epoxide. It was indeed found, that the acetate functions remained unaffected under the reaction conditions and the epoxides reduced to alcohols. The regiochemistry of the reduction was found to be structure dependent.

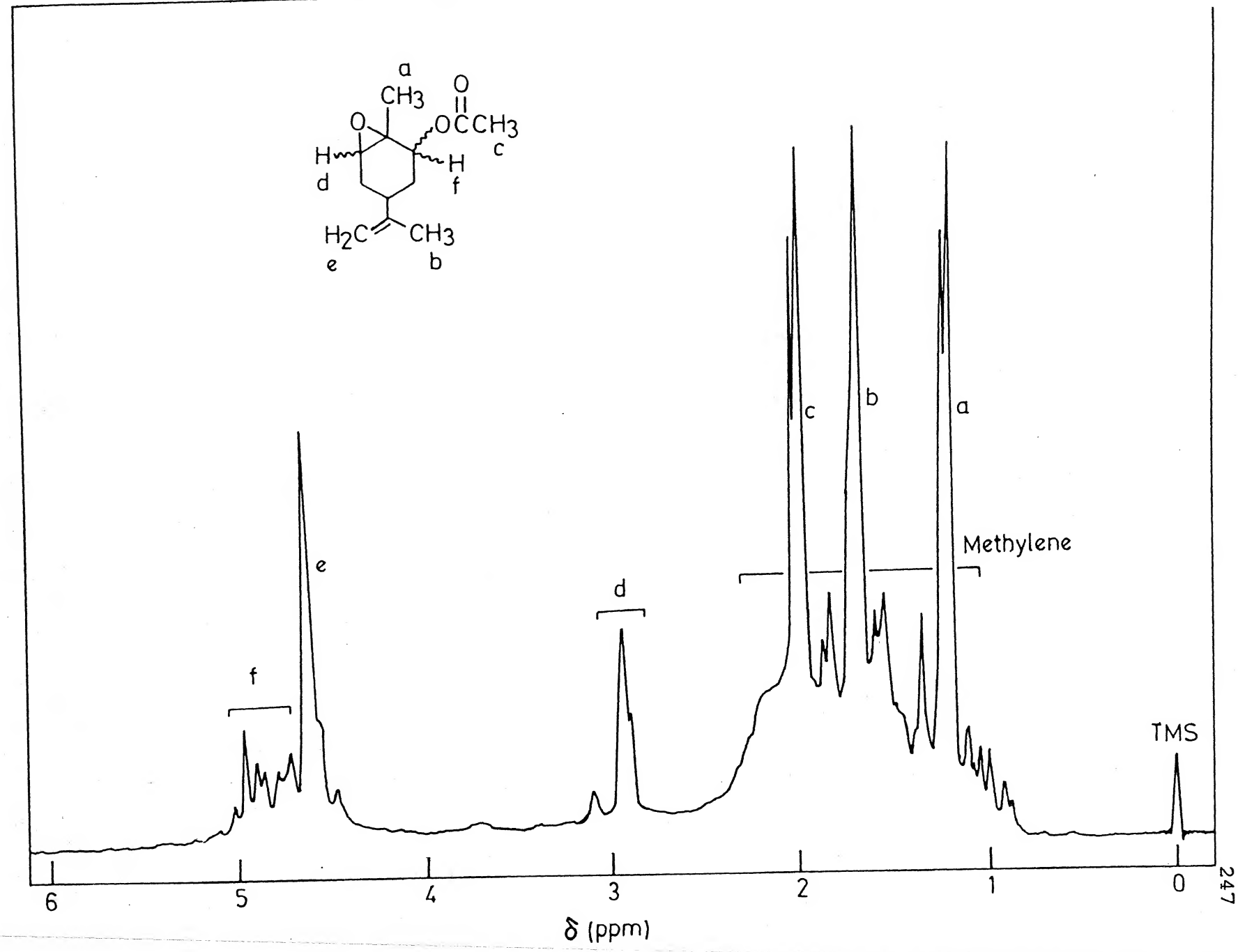
The epoxy acetate 217 was prepared as outlined in Scheme II.65. Thus, 3,5,5-trimethylcyclohex-2-en-1-one (isophrone) (221) upon reduction with $LiAlH_4$ gave the corresponding allylic alcohol 222, b.p. 96°C/20 mm in 86% yield, whose acetylation with Ac_2O-pyridine resulted in the formation of the allylic acetate 223, b.p. 92°C/11 mm in 90% yield (IR: 1740 cm^{-1}, $\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$). Its epoxidation with m-chloroperbenzoic acid yielded the epoxy acetate 217 (as a stereoisomeric mixture), b.p. 61-63°C/0.5 mm in 85% yield. The IR spectrum of this compound showed strong strong absorption at 1740 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$), ^1H NMR spectrum indicated absorptions at δ 0.9 (s, 6H, geminal $-CH_3$'s), 1.27 (s, 3H, ), 1.3-1.8 (m, 4H, CH_2's), 1.94, 1.98 (2s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 2.7 (s) and 2.9 (d, J = 2 Hz) for ) and 4.84-5.18 (m, 1H, ), and mass spectrum showed M^+ peak at 198. Appearance of two singlets for an acetoxy group and a

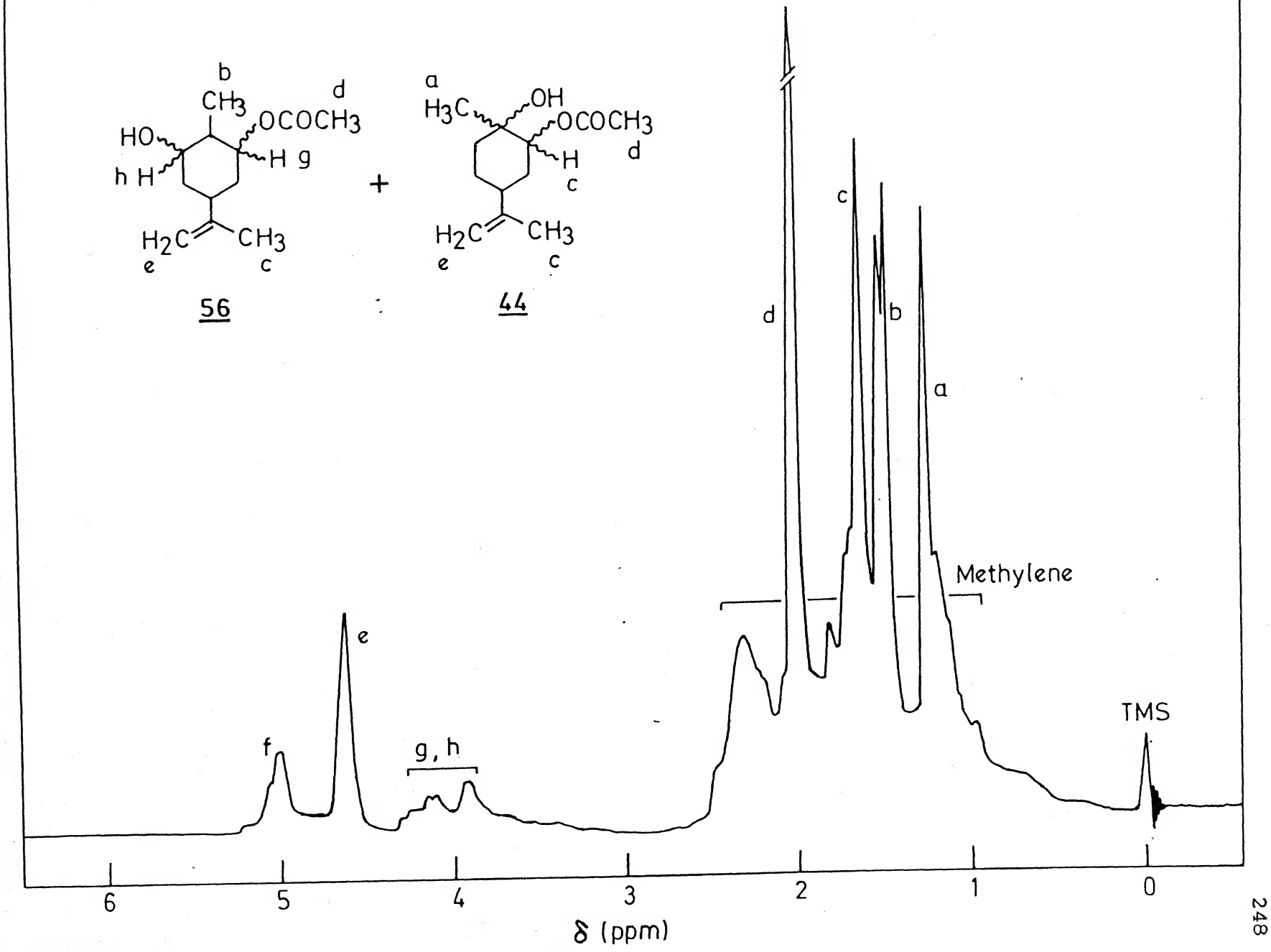

e
c
H
OCOCH3
H d
O
a
H3C
H3C
CH3
b
e
d
c
b
a
TMS
6
5
4
3
2
1
0
δ (ppm)

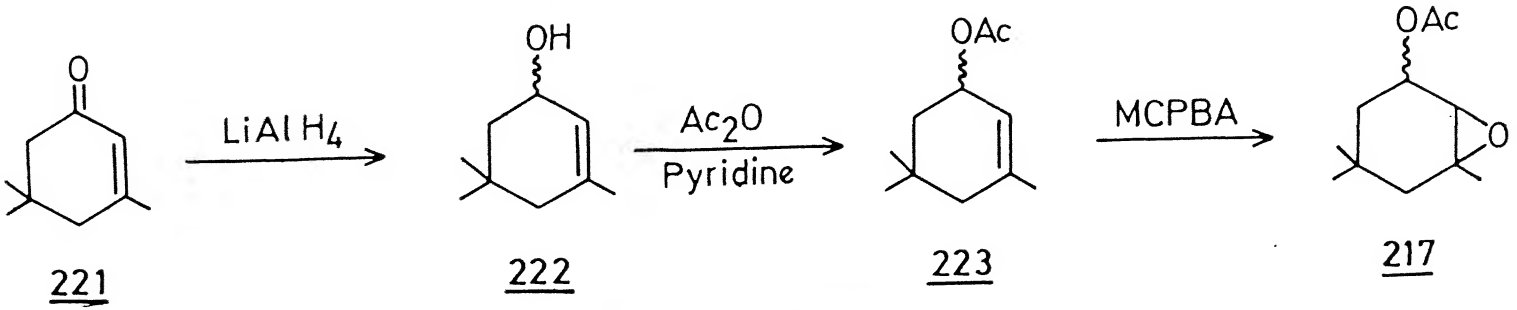

OCOCH3
H f
e
OH
a H3C
b H3C
CH3
c
d
c
b
a
TMS
f
e
6
5
4
3
2
1
0
δ (ppm)

singlet and doublet for methine proton () clearly indicated it to be a stereoisomeric mixture. Treatment of this compound with $Zn\text{-}ClSiMe_3$ followed by purification of the reaction product (by thick layer chromatography) gave 224 as a gummy liquid (Eqn. II.26, page 251), whose structure was determined by spectral means. Thus, its IR spectrum showed absorptions at 1740 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and 3500 cm^{-1} (ν_{O-H}) and its ^1H NMR showed absorptions at δ 0.8 (s, 3H, $-CH_3$), 1.11 (s, 3H, CH_3), 1.27-1.71 (m, 4H, CH_2's), 1.37 (s, 3H, ), 1.90 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 3.71 (s, 1H, $-OH$) and 5.24-5.56 (m, 1H, ). The presence of only a singlet for the methyl group at C-3 carbon and also a single multiplet for one proton for the methine () clearly indicates the product to be a single compound (3-hydroxy acetate) having the structure 224.

Epoxidation of carvone 225 with $H_2O_2/NaOH$[42] gave the epoxy ketone 226 in 80% yield. Its reduction with $NaBH_4$ followed by acetylation with Ac_2O-pyridine gave the 2,3-epoxy acetate 218 (Scheme II.66, page 250) as a stereoisomeric mixture as revealed by its ^1H NMR spectrum which showed two singlets at δ 1.20 and 1.24 for () and two singlets at δ 2.00 and 2.08 for the acetate's methyl protons ($O-\overset{O}{\overset{\|}{C}}-CH_3$). Its IR spectrum showed absorptions 1650 cm^{-1} ($\nu_{C=C}$) and at 1740 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and the mass spectrum showed M^+ peak at 210. This compound was found to be homogeneous on tlc in a variety of solvent systems and further its distillation under reduced pressure could not effect the separation of the stereoisomers. The reduction with $Zn\text{-}ClSiMe_3$ was,

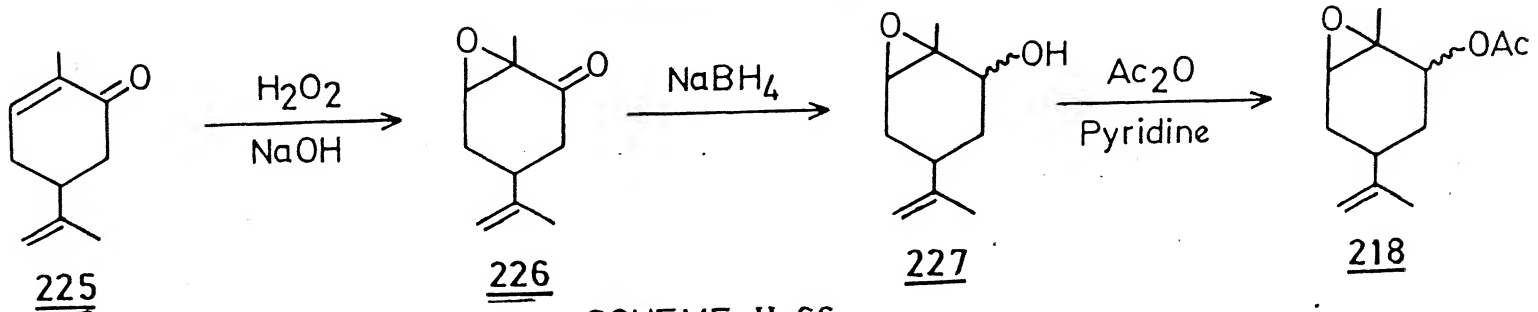

a
CH3
O
OCCH3
c
O
H
d
H
f
H2C
CH3
e
b
c
b
a
Methylene
f
e
d
TMS
6
5
4
3
2
1
0
δ (ppm)


b
CH3
d
OCOCH3
HO
H g
h H
H2C
CH3
e
c
56
+
a
H3C
OH
OCOCH3
d
H
c
H2C
CH3
e
c
44
d
c
b
a
Methylene
TMS
f
e
g, h
6
5
4
3
2
1
0
δ (ppm)



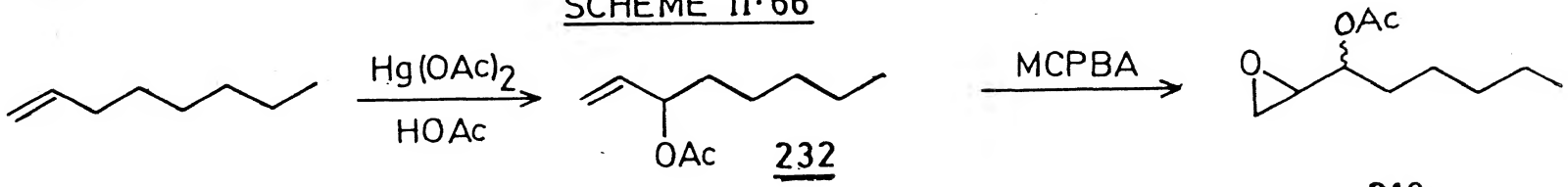
221 222 223 217

SCHEME II·65



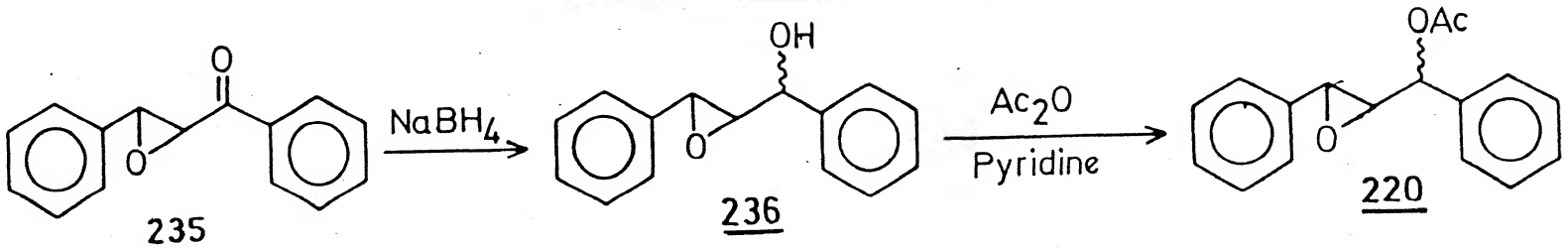
225 226 227 218

SCHEME II·66



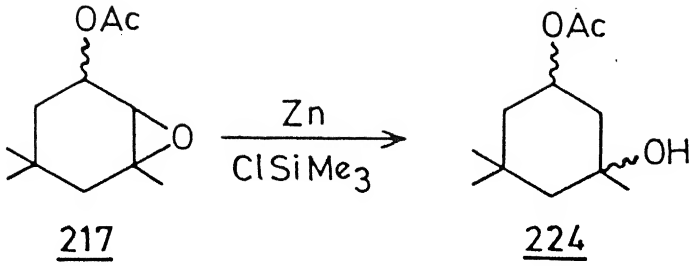
231 232 219

SCHEME II·67

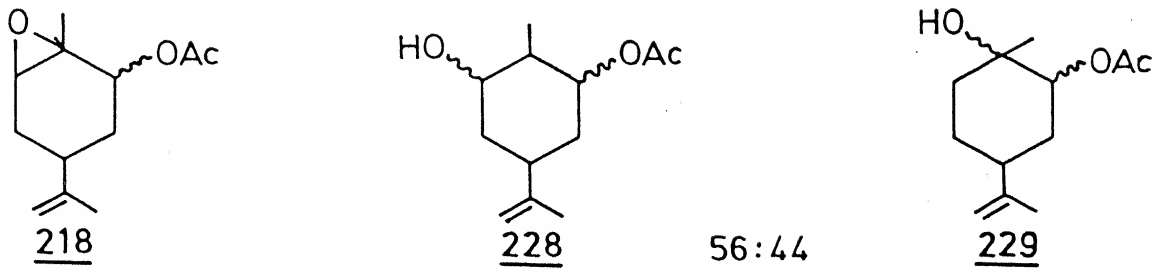


235 236 220

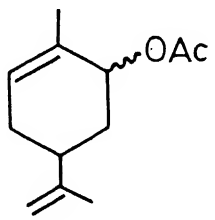
SCHEME II·68



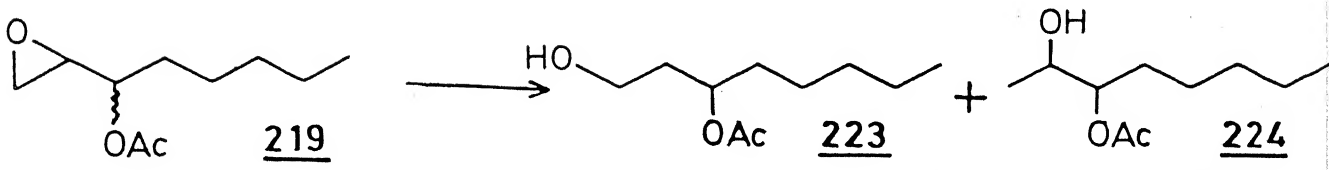
217 224 ---------- (II·26)



218 228 56:44 229

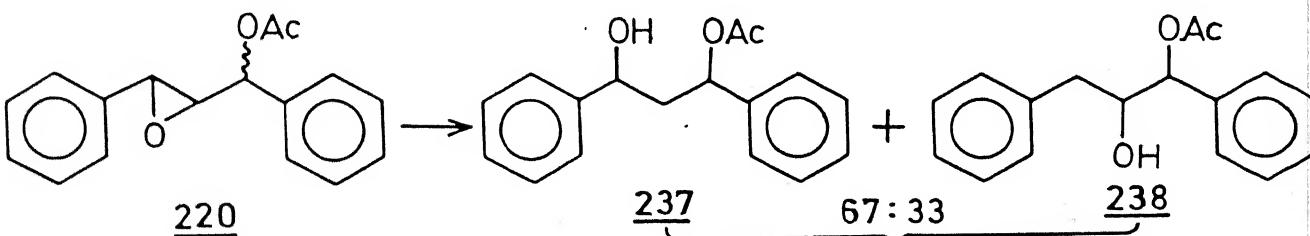


230 ------- (II·27)

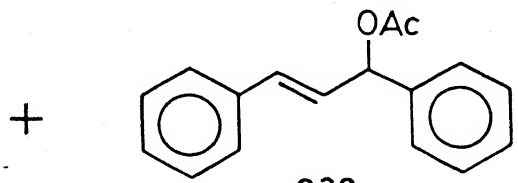


219 223 224

66:34 ------ (II·28)

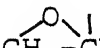
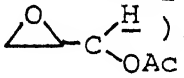


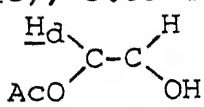
220 237 67:33 238



239 ----- (II·29)

of 229.

The next substrate taken for our study was an acyclic epoxy acetate 219 prepared by the epoxidation of the allylic acetate 229 (Scheme II.67, page250). This allylic acetate 232 was obtained by acetoxymercuration of 1-octene (231) (with $Hg(OAc)_2$ in acetic acid) in 76% yield, b.p. 80°C/20 mm (lit.[41] b.p. 190°C). Its epoxidation with m-chloroperbenzoic acid gave 219 in 80% yield, b.p. 100-102°C/10 mm. Its IR spectrum showed absorption at 1740 cm^{-1} ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$) and its ^1H NMR spectrum indicated absorptions at δ 0.9 (t, 3H, $-CH_3$, J = 7 Hz), 1.04 - 1.76 (m, 8H, CH_2's), 1.98 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$), 2.40-2.90 (m, 2H, ), 3.80 - 4.20 (m, (m, 1H, ) and 4.40 - 4.78 (m, 1H, ). Its mass spectrum showed M^+ peak at 186.

Reaction of 219 with $Zn-ClSiMe_3$ (Eqn. II.28, page 251) in the ratio 1:2.5:2 at 0°C for 25 min. gave a crude product shose purification gave a gummy liquid consisting of a mixture of the two hydroxy acetates 234 and 233 in the ratio 34:66 (combined yield 82%) (Eqn. II.28) as evidenced by its ^1H NMR spectrum. The ratio was further confirmed by its gas chromatographic analysis at 200°C (by using OV 60 column). Its IR spectrum showed absorptions at 3500 cm^{-1} (ν_{O-H}) and 1740 ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$), and its ^1H NMR showed peaks at δ 0.80-0.97 (m, $C\underline{H_3}$), 1.10-1.80 (m, CH_2's), 2.03, 2.06 (two singlets for $-O-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$), 2.40 (br,s, $O\underline{H}$, D_2O exchangable), 3.33-4.36 (m, methines a, b and methylene c), 4.66-5.03 (m, ). Once again, in this case as well, it was expected that the methine proton $\underline{H_d}$ α to -OAc group would be the most

deshielded which appeared distinctly at δ (4.66 - 5.03). A comparison of the integration for this proton with the integration for the singlet for acetoxy groups indicated the two regioisomers 234 and 232 to be in 34:66 ratio.

Yet another acyclic example studied was the epoxy acetate 220, which was prepared (Scheme II.68, page 250) by reducing chalcone epoxide 235 with $NaBH_4$ in methanol and acetylating the corresponding epoxy alcohol (m.p. 63-64°C, lit.[39] m.p. 65°C) with Ac_2O-pyridine. The epoxy acetate 220 (m.p. 90-92°C, lit.[40] m.p. 91-93°C) obtained in 90% yield upon treatment with Zn-$ClSiMe_3$ under similar condition gave two products as shown by its tlc. The product with lower R_f value was found to be a mixture of the reduced products 238 and 237 in the ratio 33:67 (Eqn. II.29, page 251), as evidenced by its ^1H NMR spectrum, which showed absorptions at 1.92, 1.96 (two singlets, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 1.90 - 2.12 (m, $Ph-\underset{OAc}{CH}-CH_2-CH(OH)Ph$), 2.42 (br,s, -OH, and $PhCH_2-$), 4.16-4.38 (m, $-\underset{OAc}{CH}(OH)-CH_2CHOAc$), 4.46-4.64 (m, $Ph-\underset{OH}{CH}-$), 4.92 (t, $Ph-\underset{OAc}{CH}-CH_2$, J = 5 Hz) and 5.58 (d, Ph-CH(OAc)-CHOH, J = 6.5 Hz). The ratio (33.67) was obtained from the relative integrations of the protons at 4.92 and 5.58. Also, the integrations of the acetate methyl protons, appearing as two doublets at δ 1.92 & 1.96, were of the same ratio.

The higher R_f compound obtained in 40% yield was identified as the allylic acetate 239. Thus, its IR spectrum showed absorptions at 1750 cm^{-1} ($\nu_{O-\overset{O}{\overset{\|}{C}}-CH_3}$) and at 1640 cm^{-1} ($\nu_{C=C}$),

and its ^{1}H NMR showed absorptions at δ 1.95 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-\underline{CH}_3$), 4.15-4.40 (m, 1H, C<u>H</u>-OAc), 4.65-4.84 (m, 1H, =C<u>H</u>-CHOAc), 5.10 (d, 1H, J = 15 Hz, PhC<u>H</u>=CH-), 7.04 - 7.40 (m, 10 H, aryl).

From the above observations it is clear that although the acetate group is intact under the reaction conditions, the regioselectivity is not pronounced and whatever selectivity is observed is highly structure dependent. Thus, compounds <u>218</u> and <u>219</u> gave the less substituted alcohols as the major products. It is likely that some stereoelectronic and steric effects operate to decide the regioselectivity.

II.B.1(iii) Experimental

The boiling points reported are uncorrected and refer to the temperature of oil bath when distillation was done using a bulb to bulb set up. Infrared spectra were recorded on Perkin Elmer model 580 and 377 infrared spectrometers. Proton magnetic spectra were recorded on Bruker WP-80 (80 MHz), Varian EM-390 (90 MHz), Varian HA-100 (100 MHz) and Jeol PMX-60 (60 MHz) instruments. The GC analyses were done on a Varian Gas Chromatograph (using 30% SE-30 column).

The solvents used were dried as described in Section II.A.1(iii). m-Chloroperbenzoic acid, the simple olefins and ketones used were procured from Aldrich Chemical Co. Potassium tert-butoxide used in the reactions was prepared from t-butanol and potassium metal. The zinc dust was activated prior to use. Chlorotrimethylsilane, purchased from Aldrich Chemical Co. was distilled prior to use.

General Procedure for the Reduction of Epoxides into Alcohols

To a rapidly stirred suspension of activated zinc dust (5.0 mg atom) in dry dichloromethane (1.0 ml) was added slowly freshly distilled chlorotrimethylsilane (5.0 mmol). After stirring the mixture for 5 min. at room temperature, was added dropwise a solution of the epoxide (2.0 mmol) in 1 ml of dry

dichloromethane. The reaction mixture was stirred for additional 2-5 minutes and then quenched with 5.0 ml of water. After stirring for another 5 min, the reaction mixture was filtered through a sintered funnel and the residue washed with dichloromethane (2 x 10 ml). The organic layer was separated from the filtrate and the aqueous layer was extracted with dichloromethane (2 x 5 ml). The organic layers were combined and washed once with water (10 ml) and then with saturated brine (10 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave the crude product which was further purified by distillation under reduced pressure using a bulb to bulb distillation set up.

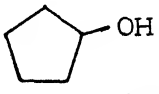
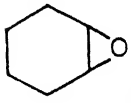
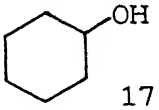
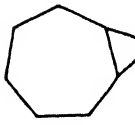
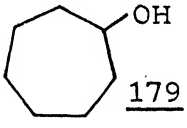
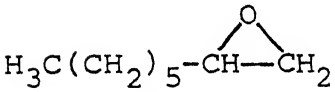
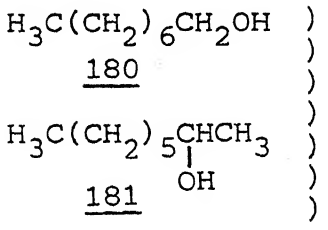
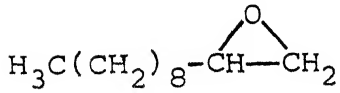
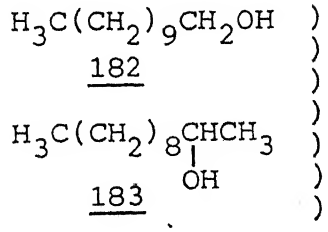
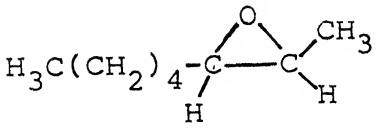
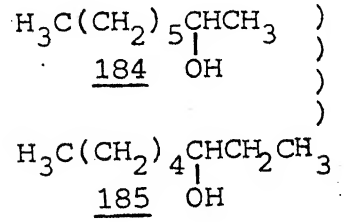
The ratio of the isomeric alcohols obtained from the unsymmetrical epoxides 174, 175 and 176 were determined by GC analysis using SE-30 column at oven temperature 200°C, by comparison with the authentic alcohols.

The yields of the alcohols, their boiling points and the relative percentages of the isomeric alcohols are summarized in Table II.5.

Preparation of the Olefinic Ketals 202a-c and 206

The olefinic ketals 202a-c and 206 were prepared from their corresponding ketones 200a-c and 204, respectively, in two stages as described below:

Table II.5 Reduction of epoxides to alcohols with Zn-ClSiMe$_3$

Epoxide	Alcohol	Yield (%)	Relative ratio[a]	IR (neat) ν_{OH} (cm^{-1})	b.p. °C /torr (lit. value)[3]
 171	 177	80	-	3360	70/25 (138)
 172	 178	98	-	3350	160-161 (161)
 173	 179	83	-	3350	95/25 (185)
 174	 180 181	88	65 35	3400	65-70/10[b]
	 182 183	96	69 31	3400	110-115/20
	 184 185	97	59 41	3380	85-90/30[b]

a, determined by gas chromatography; b, b.p. of mixture.

Stage I: Bromoketalization of ketones 202a-c and 206

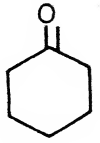
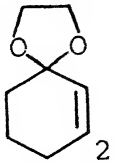
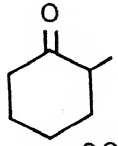
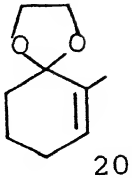
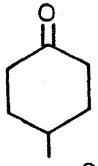
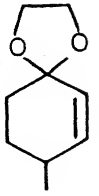
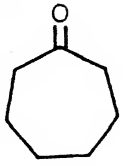
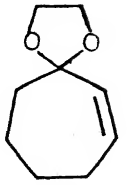
To a stirred solution of 0.05 mole of the ketone in 60 ml of distilled ethylene glycol was added at room temperature a small portion of 8.16 g (0.51 mole) of bromine taken in a dropping funnel. After stirring for 2 min. at room temperature, the rest of the bromine was added at 20°C at such a rate so as to maintain the colour of bromine in the reaction mixture. After the addition of bromine was completed, the reaction mixture was stirred for additional 15 min. and then poured into a stirred mixture of 12.5 g of anhyd. Na_2CO_3 and 50 ml pentane, followed by pouring of 50 ml water and extraction of the pentane layer. The pentane layer was then washed once with water, saturated brine solution and then dried over anhyd. Na_2SO_4. Evaporation of the pentane layer under reduced pressure gave the bromoketal.

The bromoketals 201a-c and 205 thus obtained from ketone 200a-c and 204, respectively were in each case, directly dehydrobrominated to give the corresponding olefinic ketals 202a-c and 206, respectively as described below:

Stage II: Dehydrobromination of bromoketals to olefinic ketals

Potassium tert-butoxide (8.4 g, 0.075 mole) was taken in dry dimethylsulphoxide (30 ml) and stirred at 40°C until a homogeneous solution was obtained. The bromoketal was added dropwise to the potassium tert-butoxide solution in over 20 min. at

Table II.6 Formation of olefinic ketals from ketones

Ketone	Olefinic acetal	Time (hr) Yield[a]	b.p. °C/torr (lit.value)	IR (cm^{-1}) $\nu_{C=C}$ ν_{C-O-C}	^1H NMR δ (ppm)	Mass m/e, (M^+)
 200a	 202a	7 hr 80%	73-75/15 (87-89/23)	1650 1030	1.06-2.4 (m, 6H, $-CH_2$) 3.83 (s, 4H, $-OCH_2CH_2O-$) 5.28-5.88 (m, 2H, vinylic)	140
 200b	 202b	8 hr 70%	90-92/10	1650 1040	1.2-2.3 (m, 8H, $-CH_2$) 1.62 (s, 3H, $-CH_3$) 5.71 (m, 1H, vinylic)	154
 200c	 202c	7 hr 78%	100-101/20	1650 1030	1.0 (d, 3H, J = 7 Hz, $-CH_3$) 1.42-2.32 (m, 5H, $-CH_2$ & CH) 3.84 (s, 4H, $-OCH_2CH_2O-$) 5.44 (m, 2H, vinylic)	154
 204	 206	6 hr 75%	94-95/10 (67/2.5)	1655 1070	1.4-2.5 (m, 8H, $-CH_2$) 3.8 (m, 4H, $-OCH_2CH_2O-$) 5.66 (m, 3H, vinylic)	154

a, Overall yield based on ketone

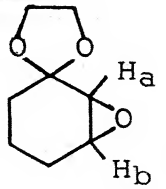
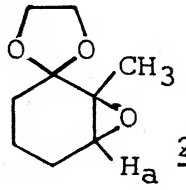
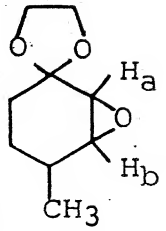
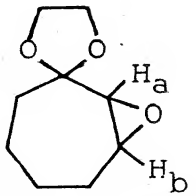
room temperature and the stirring continued till the bromo-ketal was completely reacted (as indicated by tlc). The reaction mixture was then slowly added to cold water (100 ml) with stirring and extracted with hexane (4 x 50 ml). The hexane extract was washed with water (2 x 50 ml), followed by brine (50 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure followed by distillation of the crude product gave the olefinic ketal.

The reaction times, overall yields and boiling points of the olefinic ketals 202a-c and 206 obtained in each case are summarized in Table II.6.

Epoxidation of the Olefinic Ketals

To a stirred solution of the olefinic ketal (0.01 mole) in 25 ml dry dichloromethane was added slowly a solution of m-chloroperbenzoic acid (0.011 mole) in 50 ml dry dichloromethane at $0^{\circ}C$ and the stirring continued till the epoxidation was completed (as indicated by tlc). The reaction mixture was then extracted with 5% aqueous NaOH solution (4 x 25 ml) and the organic layer washed with water (2 x 25 ml), brine (25 ml) and then dried over anhyd. Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave the crude epoxy ketal which was purified by distillation.

The time required for the reaction, the yield, and the physical data of each of the epoxy ketals 203a-c and 207

Epoxy Acetal	Time/ Yield	b.p. °C/torr	IR(cm^{-1}) ν_{C-O-C} $\nu_{\triangle O}$	^1H NMR: δ ppm	Mass, m/e (rel. ab.)
 203a	92%	100-5/2	1120 1270	1.1-2.4 (m, 6H, $-CH_2$'s) 2.73 (d, 1H, J = 4 Hz H_a) 2.64-2.79 (m, 1H, H_b) 3.53 (m, 4H, $-OCH_2CH_2O-$)	156 (46, M^+) 127 (54), 115 (39) 99 (100), 86 (57) 56 (55)
 203b	81%	110/2	1140 1260	1.16 (s, 3H, $-CH_3$) 1.04-2.32 (m, 6H, $-CH_2$'s) 2.88 (m, 1H, H_a) 3.86 (m, 4H, $-OCH_2CH_2O-$)	170 (14, M^+) 155 (42), 111 (40), 99 (100) 54 (35)
 203c	91%	90/1	1120 1275	1.08 (d, 3H, J = 7 Hz, $-CH_3$) 1.16-2.2 (m, 5H, $-CH_2$ & CH) 2.76 (m, 1H, H_a) 2.98 (m, 1H, H_b) 3.86 (m, 4H, $-OCH_2CH_2O-$)	170 (14, M^+) 155 (15), 139 (28) 135 (16), 99 (100) 55 (41)
 207	80%	80/0.5	1150 1290	1.14-2.4 (m, 8H, $-CH_2$'s) 2.74 (d, 1H, J = 5 Hz, Ha) 2.94 (m, 1H, H_a) 3.9 (m, 4H, $-OCH_2CH_2O-$)	170 (8, M^+), 113 (13), 99 (100), 86 (100) 55 (39)

C, H anal. for $C_8H_{12}O_3$ (203a): Calcd. C, 61.50; H, 7.69. Found: C, 61.39; H, 7.51.
(203b : Calcd: C, 63.53; H, 8.24. Found: C, 63.31; H, 8.17.
$C_9H_{14}O_3$ (203c): Calcd: C, 63.53; H, 8.24. Found: C, 63.33; H, 8.21.
(207) : Calcd: C, 63.53; H, 8.24. Found: C, 63.33; H, 8.19.

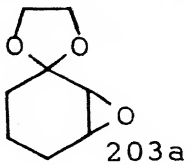
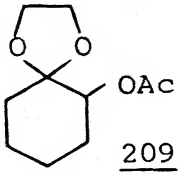
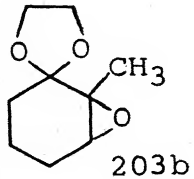
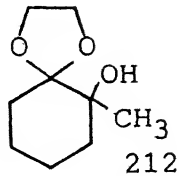
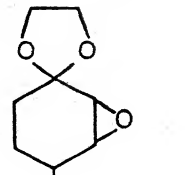
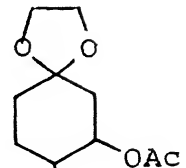
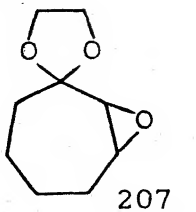
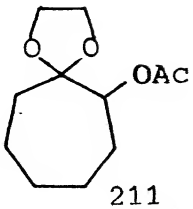
obtained by the above procedure are summarized in Table II.7.

General Procedure for the Reduction of Epoxy Ketals

To a stirred suspension of freshly activated zinc dust (0.33 g; 0.005 g-atm) in 1 ml of dry dichloromethane under dry nitrogen atmosphere was slowly added dropwise a solution of distilled chlorotrimethylsilane 0.55 g (0.55 mole) in 1 ml dry dichloromethane at room temperature. After stirring for 5 min. the reaction mixture was cooled to 0°C and a solution of the epoxy ketal (0.002 mole) in 2 ml dry dichloromethane was slowly introduced (in 5 min.) and stirring continued till the reaction was completed as indicated by tlc (10-15 mins. were required). A 10% aqueous solution of $NaHCO_3$ (5 ml) was then slowly added to the reaction mixture, stirred for 2-3 mins. and filtered through a sintered funnel. The organic layer was separated, and the aqueous layer extracted with dichloromethane (2 x 10 ml). The combined organic layers were washed with water (2 x 5 ml), brine (10 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude hydroxy ketal, which was purified as acetate as described below.

Acetylation of hydroxy ketals: The crude hydroxy ketal obtained was dissolved in 5 ml dichloromethane and to it acetic anhydride (0.2 g , 2 mmol) and pyridine (0.32 g, 4 mmol) were added and the mixture stirred for 24 hr. at room temperature. The mixture was then extracted with water (3 x 5 ml), brine (5 ml) and the

Table II.8 $Zn\text{-}ClSiMe_3$ reduction-acetylation of epoxy ketals

Epoxy acetal	Product	Overall yield[a] (%)	Reaction[b] (min)	IR (cm^{-1})	^1H NMR: δ (ppm)	Mass m/e, (M^+)
 203a	 209	82	10	1760 ($\nu_{O-\underset{\underset{O}{\|}}{C}-CH_3}$)	1.33-2.33 (m, 8H, $-CH_2$'s) 2.0 (s, 3H, $-OCOCH_3$) 3.87 (s, 4H, $-OCH_2CH_2O-$) 4.9 (dd, 1H, CH-OAc, J = 11 & 2 Hz)	200
 203b	 212	83	10	3500 (ν_{O-H})	1.29 (s, 3H, $-CH_3$) 1.36-2.36 (m, 8H, $-CH_2$'s) 3.72-4.23 (m, 4H, $-OCH_2CH_2O-$)	214
 H_3C 203c	 H_3C 215	80	15	1755 ($\nu_{O-\underset{\underset{O}{\|}}{C}-CH_3}$)	1.12 (d, 3H, $-CH_3$, J = 6.5 Hz) 1.62-1.84 (m, 7H, $-CH_2$'s & $CHCH_3$) 2.0 (s, 3H, $-OCOCH_3$); 3.7-4.1 (m, 4H, $-OCH_2CH_2O-$), 4.8-5.1 (m, 1H, CH-OAc)	214
 207	 211	84	15	1758 ($\nu_{O-\underset{\underset{O}{\|}}{C}-CH_3}$)	1.32-2.55 (m, 10 H, $-CH_2$'s) 2.02 (s, 3H, $OCOCH_3$) 3.88 (s, 4H, $-OCH_2CH_2O-$) 5.11 (dd, 1H, CH-OAc, J = 12 & 4 Hz)	214

a, For reduction followed by acetylation; b, For $Zn\text{-}ClSiMe_3$ reduction.

organic layer dried over anhyd. Na_2SO_4. The solvent was evaporated and the crude acetoxy ketal purified by thick layer chromatography (silica gel) using benzene and 5% acetone as eluent.

The epoxy ketals 203a-c and 207 were all reduced to the 2-hydroxyketals. Upon acetylation all except the 2-hydroxyketal 212 derived from 203b were acetylated to the 2-acetoxy ketals. The time required for the reduction of epoxy ketals to 2-hydroxyketals, overall yields of the 2-acetoxy ketals and their spectral data are summarized in Table II.8.

Preparation of the Epoxy Acetate (217)

To a stirred solution of isophorone 221 (0.014 g, 3.0 mmol) in 10 ml dry ether at 0°C was added a suspension of lithium aluminium hydride (0.114 g, 3.0 mmol) in 5 ml ether, in 5 min. and stirring continued for 5 hr. About 2 ml of ethyl acetate was then added, followed by 2 ml of saturated NH_4Cl solution. The mixture was stirred for 10 min, filtered, the ether layer washed with water (2 x 5 ml), brine, and dried over anhyd. Na_2SO_4. Evaporation and distillation gave the allylic alcohol 222 (yield, 0.356 g, 86%), b.p. 96°C/20 mm (lit.[43] b.p. 87-88°/11 mm).

IR (thin film), ν_{max} (cm^{-1}): 1665 ($\nu_{C=C}$), 338 (ν_{OH}).

0.3 g (2.14 mmol) of 222 was treated with acetic anhydride (0.24 g, 2.35 mmol) and pyridine (0.17 g, 4.28 mmol) in 2 ml dry dichloromethane and stirred for 12 hr. at room

temperature. To the reaction mixture was added 5 ml dichloromethane and was then extracted with water (3 x 5 ml), brine and dried the organic layer over anhyd. Na_2SO_4. Evaporation and distillation gave the allylic acetate 223, b.p. 102-103°C/10 mm (yield, 0.366 g, 94%).

IR (thin film), ν_{max} (cm^{-1}): 1735 ($\nu_{-O-\overset{O}{\overset{\|}{C}}-CH_3}$), 1665 ($\nu_{C=C}$).

0.35 g (1.92 mmol) of the allylic acetate 223 was epoxidized using m-chloroperbenzoic acid 0.36 g (2.11 mmol) at room temperature for 8 hr according to the procedure described for epoxy ketals (vide supra). Work-up and distillation gave the epoxy acetate 217 (yield, 0.323 g, 85%). Spectral and physical data are given in Table II.9.

Preparation of Epoxy Acetate (218)

Carvone 225, 1.2 g (8.0 mmol) was dissolved in 10 ml methanol and 2.3 ml (24 mmol) of 30% H_2O_2 was added to it and the mixture was cooled to 15°C (cold water bath). 0.7 ml (4.0 mmol) of 6 N aq. NaOH was slowly added with stirring during 20 min., while maintaining the temperature of the reaction mixture at 15°C. The reaction mixture was stirred for additional 4 hr at 20°C and then poured into 15 ml of water and extracted with ether (3 x 10 ml). The ether extracts were washed with water (2 x 10 ml), brine (10 ml) and dried over anhyd. Na_2SO_4. The ether eas evaporated and the product distilled (b.p. 76-77°C/5 mm) to get the epoxide 226 (yield, 1.06 g, 80%).

IR (thin film), ν_{max} (cm^{-1}) 1720 ($\nu_{C=O}$).

The epoxide 226 1.0 g (6 mmol) was dissolved in 15 ml methanol and sodium borohydride 0.114 g (3 mmol) was slowly added at 0°C. After 1 hr stirring at 0°C, the reaction mixture was pured into 20 ml water and extracted with ether (3 x 20 ml). The ether extracts were washed with water (10 ml) and brine (10 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent and distillation (b.p. 75-77°C/2 mm) gave the epoxy alcohol 227 (yield, 0.85 g, 85%).

IR (thin film), ν_{max} (cm^{-1}): 3450 (ν_{O-H}).

The epoxy alcohol 227, 0.84 g (5 mmol) in 3 ml dry dichloromethane was stirred with acetic anhydride 0.56 g (5.5 mmol) and pyridine 0.79 g (10 mmol) at room temperature for 10 hr and the reaction was worked up as in the case of 233. Distillation of the crude product gave the epoxy acetate 218 (a stereoisomeric mixture), (yield, 0.96 g, 91%) whose boiling point and spectral characteristics are given in Table II.9.

Preparation of the Epoxy Acetate (219)

A mixture of 1-octene (1.0 g, 9 mmol), mercuric acetate 4.3 g (13.5 mmol), and 5 ml of glacial acetic acid was heated at 100°C for 12 hr with vigorous stirring. The reaction mixture was then decanted (to remove mercury) and diluted with water (20 ml) and extracted with ether (3 x 10 ml). The combined ether extracts were washed with 10% $NaHCO_3$ solution (3 x 10 ml),

brine (10 ml), and dried over anhyd. Na_2SO_4. Evaporation of solvent and distillation gave 3-acetoxy-1-octene (232), b.p. 80°C/20 mm (lit.[41] b.p. 190°C) (yield: 1.16 g, 76%).

IR (thin film), ν_{max} (cm^{-1}): 1650 ($\nu_{C=C}$), 1750 ($\nu_{O-\overset{O}{\overset{\|}{C}}-}$).

PMR (CCl_4), δ (ppm): 0.9 (t, 3H, $-CH_2\underline{CH_3}$, J = 7 Hz), 1.12-1.80 (m, 8H, ($-CH_2$), 2.08 (s, 3H, $O-\overset{O}{\overset{\|}{C}}-CH_3$), 4.35-4.56 (m, 1H, $-CH-OCOCH_3$).

To 3-acetoxy-1-octene (232), 1.02 g (6 mmol) in 15 ml dichloromethane was added m-chloroperbenzoic acid 1.14 g (6.6 mmol) and the mixture stirred for 6 hr at room temperature. The reaction was worked up as in case of epoxy acetate (vide supra). Distillation of the product at b.p. 100-102°C/10 mm gave the epoxy acetate 219 (yield, 0.98 g, 80%). The spectral characteristics of 219 are given in Table II.9.

Preparation of Epoxy Acetate (220)

To a stirred solution of chalcone epoxide 235, 1.12 g (5 mmol) in 15 ml methanol at 0°C, was added 0.095 g (2.5 mmol) of sodium borohydride and stirring continued for 1 hr at 0°C. The reaction was then worked up as in the case of epoxy alcohol 227. The crude product was recrystallized from benzene-hexane mixture to give the epoxy alcohol 236 (mixture of erythro and threo isomers), m.p. 63-65°C (lit.[39] m.p. 65°C) (yield, 1.03 g, 93%).

IR (KBr), ν_{max} (cm^{-1}): 3400 (ν_{O-H}).

Table II.9 Physical and spectral data of epoxy acetates

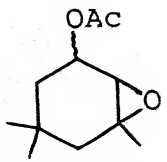
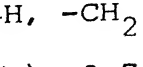
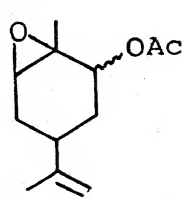
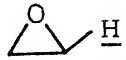
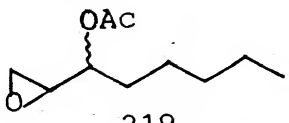
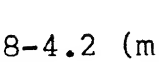
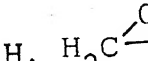
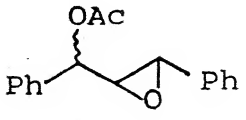
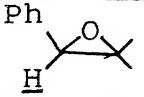
Compound	b.p. °C/torr or m.p. (lit. value)	IR (cm^{-1})	Mass m/e (M^+)	^1H NMR: δ ppm
1	2	3	4	5
 217	61-3/0.5	1750 ($\nu_{-\overset{O}{\overset{\|}{C}}CH_3}$)	198	0.9 (s, 6H, gem. CH_3's), 1.27 (s, 3H, ), 1.3-1.8 (m, 4H, $-CH_2$'s), 1.94 & 1.98 (2s, $OCOCH_3$), 2.7 (s) & 2.9 (d, J = 2 Hz) (for ), 4.84-5.18 (m, 1H, CH-OAc).
 228	83-5/1.0	1650 ($\nu_{C=C}$) 1740 (ν_{-OCCH_3} ‖ O)	210	0.9-2.30 (m, 5H, 2 CH_2's and allylic methine), 1.2 & 1.24 (2s, ), 2.00 & 2.08 (2s, $OCOCH_3$), 2.94 (t, 1H, H_3C  , J = 2 Hz), 4.6 (s, 2H, $>CH_2$), 4.44-5.10 (br,m, 1H, CH-OAc)
 219	110-2/10	1745 (ν_{-OCCH_3} ‖ O)	186	0.9 (t, 3H, CH_2-CH_3, J = 7 Hz), 1.04-1.76 (m, 8H, CH_2's), 1.98 (s, 3H, $-OCOCH_3$), 2.40-2.90 (m, 2H, ), 3.8-4.2 (m, 1H, H_2C ), 4.4-4.78 (m, 1H, CH-OAc)

Table II.9 (contd.)

1	2	3	4	5
	90-2 (91-3)[40]	1740 ($\nu_{OCCH_3}^{O}$)	268	2.08 & 2.12 (2s, 3H, OCOC<u>H</u>$_3$), 3.04-3.28 (m, 1H, ), 3.6-3.8 (1H, ), 5.62 5.62 & 5.74 (2d, 1H, C<u>H</u>-OAc, J = 6 Hz & 5 Hz, respectively), 7.1 & 7.22 (2s, 10 H, aryl)

C, H Anal. for $C_{11}H_{18}O_3$, <u>217</u> : Calcd: C, 66.67; H, 9.09. Found: C, 66.52; H, 8.99.
$C_{12}H_{18}O_2$, <u>228</u> : Calcd: C, 68.57; H, 8.57. Found: C, 68.50; H, 8.51.
$C_{10}H_{18}O_3$, <u>219</u> : Calcd: C, 64.52; H, 9.68. Found: C, 64.44; H, 9.54.
$C_{17}H_{16}O_3$, <u>220</u> : Calcd: C, 76.12; H, 5.97. Found: C, 75.92; H, 5.87.

The epoxy alcohol 236, 0.9 g (4 mmol) in 3 ml dichloromethane was stirred with acetic anhydride 0.41 g (4 mmol) and pyridine 0.6 g (8 mmol) for 20 hr at room temperature. The reaction was worked up as in the case of 233. Recrystallization of the product from ethanol gave the epoxy acetate 220 (stereoisomeric mixture), m.p. 90-92°C (lit.[40] m.p. 91-93°C). The spectral characteristics of 220 are given in Table II.9.

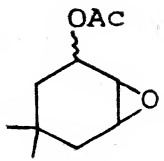
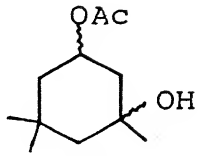
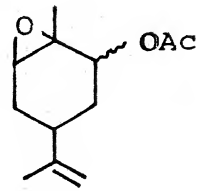
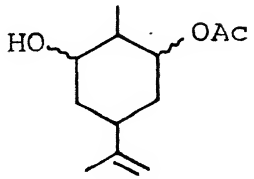
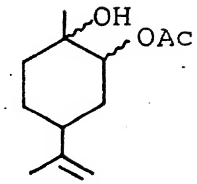
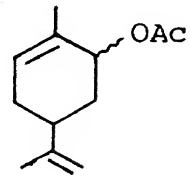
General Procedure for the Reduction of Epoxy Acetates (217-220)

To a stirred suspension of zinc dust 0.2 g (6 mg atom), in 1 ml dry dichloromethane under dry nitrogen atmosphere was slowly added dropwise, in 5 min., a solution of freshly distilled chlorotrimethylsilane (0.55 g, 5 mmol) in 1 ml dry dichloromethane at room temperature. After stirring for additional 5 min, the reaction mixture was cooled to 0°C and a solution of the epoxy acetate (2 mmol) in 2 ml dry dichloromethane was slowly introduced in 5 min. and stirring continued till the reaction was complete (the times required for individual epoxy acetates are given in Table II.10). About 4 ml of water was then added slowly to the reaction mixture, stirred for additional 5 min. The mixture was filtered, residue washed with dichloromethane (2 x 10 ml) and the organic layer from the filtrate was separated. It was then washed with water (3 x 5 ml), brine (5 ml) and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crude product/s obtained as gummy substances in all cases were separated by thick layer chromatography using benzene-acetone

(90:10) mixture as eluent.

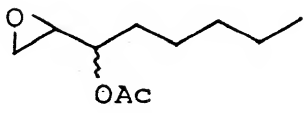
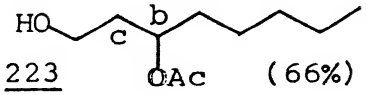
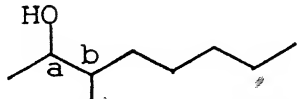
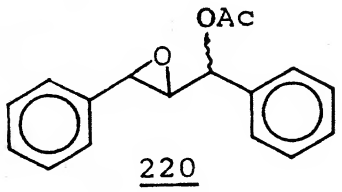
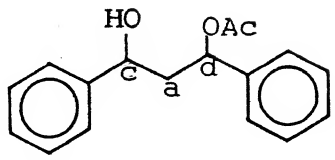
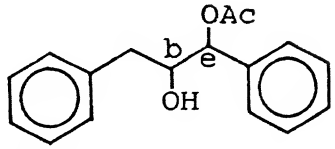
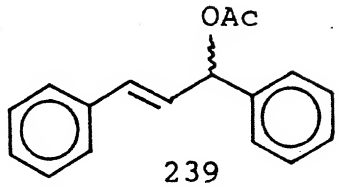
The yields of the product/s obtained in each case and their spectral data are summarized in Table II.10. The relative ratios of the isomeric products which were obtained as inseparable mixtures (from epoxy acetates 218-220) after thick layer chromatographic separation were determined from the integration values (of protons HO-$\underline{C}$H-$\overset{1}{C}$H-$\overset{1}{\underline{C}}$H-OAc and HO$\underline{C}$H-$CH_2$-$\underline{C}$H-OAc) or their ^{1}H NMR spectra. The relative percentages thus determined were further confirmed by GC analysis.

Table II.10 Reduction of epoxy acetates with $Zn\text{-}ClSiMe_3$

Epoxy acetate	Time (min)	Product/Products (& Rel. percentage)	Yield (%)	IR (cm^{-1}) ν_{O-H} ν_{O-C-} (=O)	^1H NMR ($CDCl_3$) δ ppm	Mass m/e (M^+)
1	2	3	4	5	6	7
 217	20	 224	70	3500, 1740	0.8 & 1.11 (2s, 6H, $C(C\underline{H}_3)_2$), 1.27-1.71 (m, 4H, CH_2's), 1.37 (s, 3H, HO-C-$C\underline{H}_3$), 1.9 (s, 3H, $COC\underline{H}_3$), 3.71 (s, 1H, $O\underline{H}$), 5.24-5.26 (m, 1H, $C\underline{H}$-OAc)	200
 218	30	 228 (56:44)  229	60	3500, 1735, 1650 ($\nu_{C=C}$)	1.55 (s, C(OH)$C\underline{H}_3$), 1.6 (d, CH-$C\underline{H}_3$), 1.95 (s, $COC\underline{H}_3$), 3.53-4.45 (m, $C\underline{H}_b$-OAc & $C\underline{H}$-OH), 4.73 (s, 2H, $=CH_2$), 5.01-5.30 (m, HO-CH-$C\underline{H}$-OAc)	212
 230	30		30	1650 ($\nu_{C=C}$), 1750	1.42 (s, 6H, 2 =-CH_3's), 2.08 (s, 3H, $OCOC\underline{H}_3$); 1.10-1.99 (m, 5H, 2CH_2's	194

...contd.

Table II.10 (contd.)

1	2	3	4	5	6	7
					& C-H), 3.72-3.91 (m, 1H, CH-OAc), 4.57 (s, 2H, $=CH_2$), 4.86-5.17 (m, 1H =C-H).	
 219	25	 223 (66%)  224 (34%)	82	3450, 1740	0.80-0.97 (m, $-CH_3$), 1.10-1.80 (m, $-CH_2$'s), 2.03-2.06 (2s, $-OCOCH_3$), 2.40 (br,s, OH), 3.33-4.36 (m, CH a,b & CH_2,c), 4.66-5.03 (m, CH_d)	188
 220	10	 (67 : 33) 	50	3400, 1750	1.92, 1.96 (2s, $OCOCH_3$), 1.90-2.12 (m, CH_2a), 2.42 (br,s, -OH & $PhCH_2$), 4.16-4.38 (m, $-CH_b$), 4.46-4.64 (m, CH_c), 4.92 (t, CH_d, J = 5 Hz), 5.58 (d, CH_e, J = 6.5 Hz)	270
 239			40	1640 ($\nu_{C=C}$), 1750	1.95 (s, 3H, $OCOCH_3$), 4.15-4.40 (m, 1H, CH-OAc), 6.10 (d, 1H, PhCH=, J = 15 Hz), 7.04-7.40 (m, 10 H, aryl)	252

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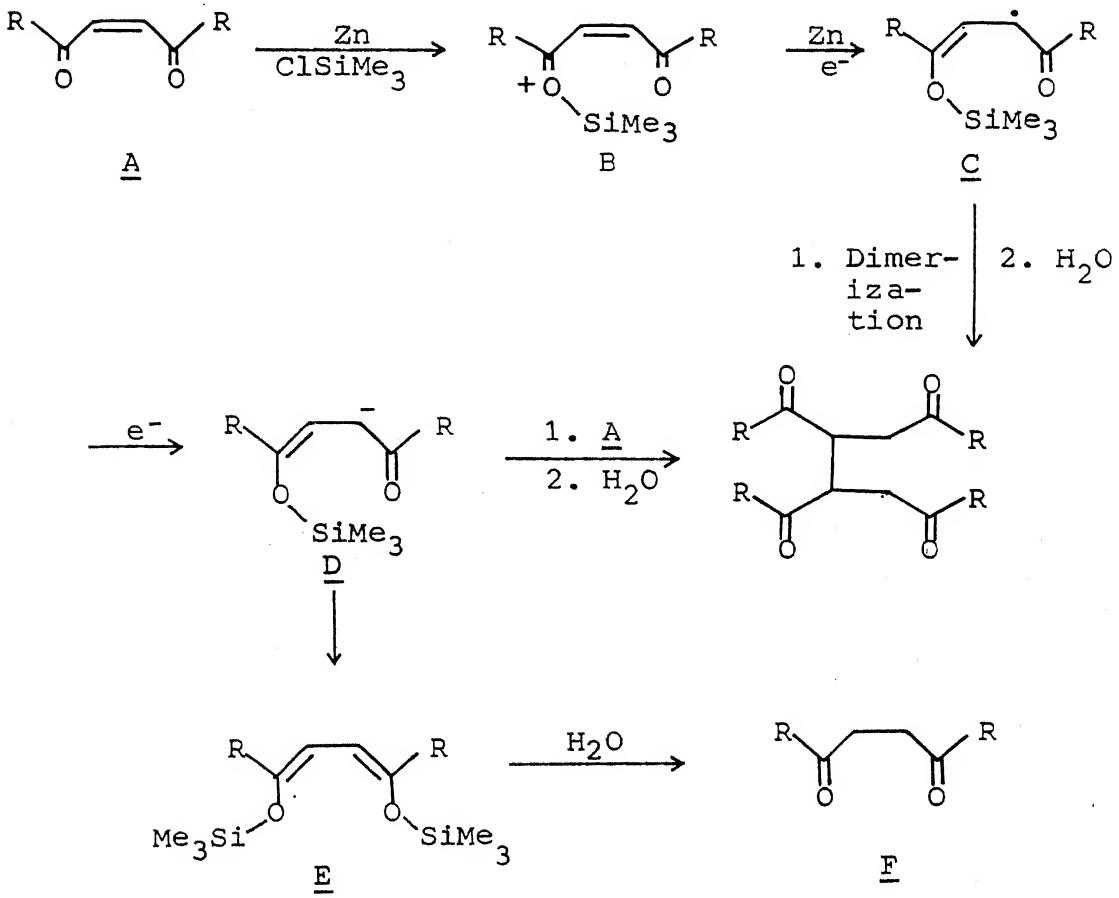
II.B.2 Reduction of Conjugated Ene-Diones

II.B.2(i) Present Work

Reduction of conjugated ene-diones to 1,4-diketones with $NaI-BF_3.Et_2O$ has been described in part A of this chapter (Sec. II.A.4). Similar reduction was found to take place with the $Zn-ClSiMe_3$ system as well, although the yields of the reduced products in this case were lower than those obtained in the case of $NaI-BF_3.Et_2O$ (cf. Tables II.4 and II.11). The same examples i.e., 130 to 134 were taken for the present study and the results are reported in Table II.11. However, the reaction of the ene-diester, diethylmaleate (134), with zinc-$ClSiMe_3$ failed to give the reduced product diethylsuccinate (141) unlike in the case of $NaI-BF_3.Et_2O$ reagent system.

The probable mechanism for the reduction of ene-diones with $Zn-ClSiMe_3$ is outlined in Scheme II.69. Initial complexation of $ClSiMe_3$ with one of the carbonyl oxygens of the ene-dione A, followed by stepwise electron transfer would lead to an intermediate E, through various other intermediates B, C and D, which eventually upon work-up leads to the 1,4-diketone F. It is likely that the intermediate C dimerises under the reaction conditions and perhaps further undergoes some transformations thus decrease in the yield of the 1,4-diketone F being observed. In fact, the crude product of the reaction did seem to contain some other uncharacterised products in

minor amounts besides the expected 1,4-diketone. The formation of other side products was minimized by performing the reaction at a lower temperature ($-10^{o}C$).



SCHEME II.69

II.B.2(ii) Experimental

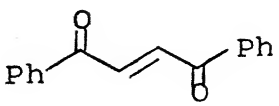
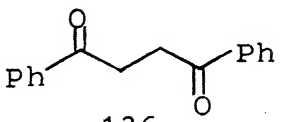
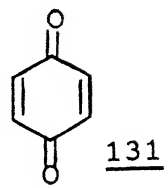
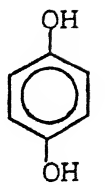
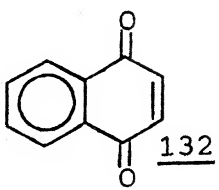
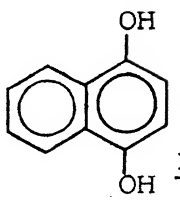
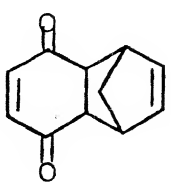
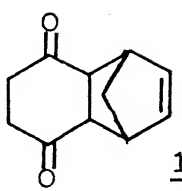
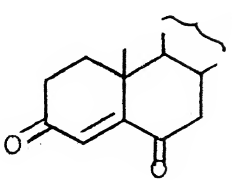
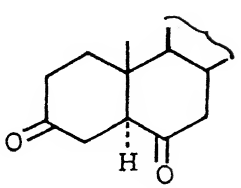
The instruments used, drying of solvent and preparation of the starting materials are the same as mentioned in Section II.A.4(iii).

General Method for the Reduction of Conjugated 1,4-Diketones with $Zn-ClSiMe_3$

To a stirred suspension of zinc dust in 1 ml of dry dichloromethane, under dry nitrogen atmosphere, was added chlorotrimethylsilane (equivalents of zinc dust and chlorotrimethylsilane in each case are mentioned in Table II.11) in 1 ml dry dichloromethane at room temperature during 5 min., and the reaction mixture stirred for additional 10 minutes. The resulting mixture was cooled to $-10^{\circ}C$ and the dione (0.5 mol) in 1 ml dry dichloromethane slowly added in 5 min., and the stirring continued for additional time (cf. Table II.11). The reaction mixture was then treated with 5 ml cold water, stirred for 5 minutes and filtered. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x10 ml). The combined organic layers were washed with water (2 x 10 ml), followed by brine and then dried over anhyd. Na_2SO_4. Evaporation of solvent gave the crude product which was further purified by thick layer chromatography.

The reduced products 136 to 140 thus obtained showed the same physical and spectral characteristics as those obtained by the NaI-BF_3.Et_2O method (cf. Sec. 11.A.4). The yields and m.ps./b.ps. of the products obtained are summarized in Table II.11.

Table II.11 Reduction of conjugated Ene-diones with Zn-$ClSiMe_3$

Substrate	Product	Molar equiv. Zn	Molar equiv. $ClSiMe_3$	Time (min.) (at -10°C)	Yield (%)	m.p.°C (lit. value)[a]
 130	 136	3	2.5	10	60	144 (145)
 131	 137	3	2.5	30	50	170 (171)
 132	 138	2.5	2.5	25	62	176 (176)
 133	 139	3	2.5	20	51	b
 134	 140	3	2.5	30	62	170-171 (172)

a, Literature references are the same as in Table II.4. b, Obtained as thick liquid.

LIST OF PUBLICATIONS

1. Zinc-chlorotrimethylsilane: A novel reducing system for the conversion of epoxides into alcohols,
   Y.D. Vankar, P.S. Arya and C.T. Rao,
   Synthetic Communcations, 13(10), 869 (1983).

2. Sodium iodide - Borontrifluoride etherate: A mild reagent for the conversion of benzylic and allylic alcohols into iodides and sulphoxides into sulphides,
   Y.D. Vankar and C. Trinadha Rao,
   Tetrahedron Lett., 26 (22), 2717 (1985).

3. Reaction of sulphoxides and nitriles in the presence of trifluoroacetic anhydride and trifluoroacetic acid: A case of Ritter reaction on Pummerer intermediate,
   Y.D. Vankar and C. Trinadha Rao,
   Tetrahedron, 41, 3405 (1985).

4. Selective cleavage of benzyl ethers using sodium iodide-boron trifluoride etherate reagent system,
   Y.D. Vankar and C. Trinadha Rao,
   J. Chem. Res., 232 (1985).

5. Sodium iodide-chlorotrimethylsilane (or boron trifluoride etherate) or zinc-chlorotrimethylsilane: Mild reagent systems for the conversion of ene-diones into 1,4-diketones,
   Y.D. Vankar, G. Kumarvel, N. Mukerjee and
   C. Trinadha Rao,
   Synthetic Communications (submitted)

6. Ritter reaction on cyclopropyl ketones and cyclopropyl carbinols,
   (to be submitted).

7. Observation of remarkable regioselectivity in the reduction of 2,3-epoxyacetals with zinc-chlorotrimethylsilane and lithium aluminium hydride,
   (to be submitted).

Vitaé

Born on October 13, 1958 in Tanuku (Andhra Pradesh), Chitturi Trinadha Rao had his early education at Delhi and Cochin and completed his schooling at Central School, Visakhapatnam. He obtained the degree of Bachelor of Science from A.V.N. College, Visakhapatnam (Andhra University) in 1978, and the degree of Master of Science from the Andhra University (Visakhapatnam) in 1980.

He joined the Ph.D. programme in the Department of Chemistry, Indian Institute of Technology, Kanpur in January 1981. In April 1985 he joined the Oil & Natural Gas Commission (ONGC), Madras, as Class I Officer, where he is presently continuing.